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Title:

Small volume plasma exchange for Guillain-Barré syndrome in resource-limited settings: a safety and feasibility study

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ABSTRACT

OBJECTIVE

To assess the safety and feasibility of small volume plasma exchange (SVPE) as an alternative to standard plasma exchange (PE) or intravenous immunoglobulin (IVIg) for Guillain-Barré syndrome (GBS) patients.

DESIGN

Non-randomized, single arm, interventional trial.

SETTING

National Institute of Neurosciences and Hospital, Dhaka, Bangladesh.

PARTICIPANTS

Twenty adult (>18 years) patients with GBS presented within 2 weeks of onset of weakness who were unable to walk unaided for more than 10 meters.

INTERVENTIONS

SVPE involves blood cell sedimentation in a blood bag and removal of supernatant plasma after blood cells are re-transfused. This procedure was repeated three to six times a day, for eight consecutive days.

OUTCOME MEASURES

Serious adverse events (SAE) were defined as severe sepsis and deep venous thrombosis related to the central vein catheter (CVC) used during SVPE. SVPE was considered safe if less than 5/20 patients experienced a SAE, and feasible if 8 L plasma could be removed within 8 days in at least 15/20 patients.

RESULTS

Median patient age 33 years (IQR 23-46; range 18-55); 13 (65%) were male. Median MRC sum score was 20 (IQR 0-29; range 0-36); three (15%) patients required mechanical ventilation. One patient developed SAE (severe sepsis, possibly related to CVC). Minor adverse effects were

transient hypotension in 10 (50%) patients; CVC-associated bleeding in 10 (50%); transfusion reaction to fresh frozen plasma in 4 (20%); and hypo-albuminemia, anaemia or electrolyte imbalance in 4 (20%). Removal of 8 L plasma was possible in 15 (75%) patients. GBS disability score improved by at least one grade in 14 (70%) patients four weeks after SVPE started. No patients died.

CONCLUSION

SVPE seems a safe and feasible alternative treatment to standard PE or IVIg for GBS; further studies of clinical efficacy in low-resource developing countries are warranted.

TRIAL REGISTRATION

Clinicaltrials.gov NCT02780570 on May 23, 2016

Strength and limitations of the study:

1. The strength of this study underlies the novel and simple technique of SVPE, which is much less expensive than conventional immunotherapies (plasma exchange and intravenous immunoglobulin)
2. SVPE is corroborated as safe and feasible for the first time in a prospective and standardized cohort of patients with Guillain-Barré syndrome (GBS).
3. The intrinsic limitations of this study are its non-randomized, single arm nature, which is conducted in a single center with a limited sample size of GBS patients.
4. Clinical efficacy of SVPE on patients with GBS was a secondary end-point assessment and therefore deserves a randomized controlled trial in future to assess the clinical efficacy of SVPE for the patients with GBS.

Introduction

Guillain-Barré syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy with a yearly incidence of 1.2 to 2.3 cases per 100,000 per year [1]. GBS is characterized by rapidly progressive limb weakness and, in a proportion of cases, respiratory failure (25%) or severe autonomic dysfunction (10%). Plasma exchange (PE) was the first treatment proven to be effective for GBS, if given within 4 weeks of the onset of weakness [2-10]. Later studies showed treatment with intravenous immunoglobulin (IVIg) (0.4 g/kg per day for 5 days) has a similar efficacy as PE in patients with GBS who are unable to walk, if started within 2 weeks of the onset of weakness [11, 12].

Unfortunately, most patients in low-income countries cannot afford expensive treatment with either PE or IVIg [13]. In Bangladesh, a full course of IVIg for a 60 kg adult costs approximately 12,000-16,000 US$ and treatment with conventional PE for 5 days costs approximately 4,500-5,000 US$. The mean income in Bangladesh was 4 US$ per day in 2016 (World Bank and Bangladesh Bureau of Statistics 2016); IVIg and PE cost the equivalent of 3,000 and 1,250 mean income days, respectively. At present, the majority (92%) of patients with GBS in Bangladesh receive supportive care only [13]. In addition, mobile PE equipment is not available in Bangladesh; therefore, patients admitted to the intensive care unit (ICU) cannot receive PE. We previously reported the mortality rates for GBS in Bangladesh range from 12 to 14% and observed 29% of patients with GBS in Bangladesh are unable to walk at 6 months after onset; these poor outcomes are undoubtedly due to the low rates of specific treatment with PE or IVIg [14, 15].

Small volume plasma exchange (SVPE) may represent a cheap, effective alternative treatment for GBS. SVPE is based on the same principle as conventional PE (selective removal of plasma) but uses a novel, simple technique with much lower costs (approximately 500 US$). The current non-

randomized trial was designed to investigate the safety and feasibility of SVPE in 20 patients with GBS admitted to the National Institute of Neurosciences Hospital in Dhaka, Bangladesh.

Methods/Design

Study design

For this non-randomized, single arm, interventional safety and feasibility trial, 20 adult patients with GBS were enrolled between March 2016 and December 2016 for SVPE at the National Institute of Neurosciences and Hospital (NINS), Dhaka, Bangladesh. A detailed study protocol was published previously and includes definitions of all variables used in this study [16].

Four to six daily sessions of whole blood sedimentation and removal of supernatant plasma after re-transfusion of the sedimented blood cells was planned for the 20 patients with GBS, with a target of removing an overall volume of at least 8 litres (L) of plasma over a total of 8 days [16]. (See supplementary video for SVPE procedure)

Patients with GBS were monitored according to a standard protocol throughout the course of SVPE until the second day after withdrawal of the central venous catheter (CVC) in order to assess predefined measures of safety and feasibility and followed up for six months to assess neurological outcome. The protocol was reviewed and approved by the institutional research and ethics review committees at the icddr,b and registered at clinicaltrials.gov (NCT02780570) [16]. All patients provided written informed consent to participate in this study.

Patient and Public Involvement

Patients and or public were not involved either in the development of the research question, study design and outcome measure or recruitment to and conduct of the study.

Inclusion and exclusion criteria for patients with GBS

Patients aged ≥ 18-years-old fulfilling the diagnostic criteria for GBS of the National Institute of Neurological and Communicative Disorders and Stroke (NINDS) [17] were enrolled, provided they were unable to walk unaided for more than 10 meters (GBS disability score ≥ 3), presented within 2 weeks of the onset of weakness, and were unable to afford standard treatment with IVIg or PE. Patients with concomitant severe or terminal illnesses, evidence of healthcare-associated infection (HAI) on admission (except for aspiration pneumonia), a previous history of severe allergic reactions to properly matched blood products, and pregnant women were excluded from the study.

Control cohort

To compare the safety of SVPE in patients with GBS in the context of the background risk of central line-associated blood stream infection (CLABSI) at our institution, we prospectively assessed the incidence of CLABSI in a hospital control group of 24 adult patients without GBS receiving neurocritical care. Hospital controls were eligible based on the following characteristics: ≥ 18-years-old, a neurological diagnosis other than GBS, and a CVC placed for > 2 and ≤ 8 calendar days after admission to the same ICU or HDU unit as the SVPE-treated patients. Patients with a HAI (except aspiration pneumonia) and pregnant women were excluded from the control group.

Primary and secondary outcome measures

The primary outcome measures of safety were the number of patients with GBS treated with SVPE who developed either severe sepsis or septic shock due to CLABSI [18] and the occurrence of venous thrombosis in the limb where the CVC was placed. The primary outcome measure of feasibility was the ability to remove at least 8 L of plasma over 8 days.

The secondary outcome measures of the safety of SVPE were the relative risk of CLABSI due to SVPE (compared to CLABSI in the hospital control group without GBS), hemodynamic instability during the SVPE procedure, and development of anaemia (Hb < 8 gm/dL) or any catheter-related haemorrhage requiring a blood transfusion.

The secondary outcome measure of feasibility of SVPE was the rate of CVC occlusion during the SVPE procedure. In addition, neurological outcome was assessed using the GBS disability score [19], MRC sum score [20], Overall Neuropathy Limitation Scale (ONLS) [21] and Rasch-built Overall Disability Scale (R-ODS)[22] at 1st , 2nd , 3rd , and 6th months from the start of SVPE.

Procedure safety and documentation

Strict aseptic procedures were followed to prevent CLABSI [23-25]. SVPE was documented in terms of the duration and amount of plasma removed in each session, and the type and volume of replacement fluid and fresh frozen plasma (FFP) used. Throughout the procedure, the haemodynamic, haematological, biochemical, coagulation and infection profiles of the SVPE-treated patients were monitored according to the protocol [16]. Screening for hepatitis B and C viruses, human immunodeficiency virus (HIV) and syphilis were performed as patient baseline assessments, and also on donor FFP before administration. CLABSI, primary and secondary bloodstream infections [18], catheter-associated urinary tract infection (CAUTI) [26], ventilator-associated pneumonia (VAP) [27] and other HAI [28, 29] were documented in the SVPE-treated patients with GBS and the hospital control group.

Sample size

This safety and feasibility study enrolled 20 patients with GBS for SVPE. We could not perform a formal power calculation for this safety and feasibility study. The sample size was based on previous pilot studies conducted in GBS[30, 31] . The baseline rate of CLABSI

was measured in the hospital control group of 24 patients without GBS admitted to the same study facility who required a CVC for at least 8 days during the study period.

Stopping rules for the trial based on safety and feasibility

Decision to stop the SVPE trial was designated using a Bayesian approach [32-34]. Accordingly, a predictive success rate of 75% was predefined for the SVPE procedure. If more than 5 of 20 patients experienced an SAE, or if it appeared impossible to remove at least 8 L of plasma over 8 days in at least 15 of 20 patients, the procedure was considered unsafe or unfeasible.

Statistical analysis

The rate of HAIs (CLABSI, VAP and CAUTI) per 1000 device days were calculated by dividing the number of each HAI during the study period by the number of device days and multiplying the result by 1000. The infection safety profile for SVPE was assessed by calculating the standardized infection ratio to define the risk of HAIs in patients with GBS treated with SVPE. The standardised infection ratio (SIR) was calculated by dividing the number of observed HAI by the number of HAI predicted (i.e., the infection rate in the control group). The predicted HAI rate was calculated using the rates of HAI in the hospital control group of patients without GBS during the study period. Percentage values were compared using the Chi-square test or Fisher's exact test (two-tailed) and median values, the Mann-Whitney U-test using SPSS 22 software (IBM SPSS Statistics for Windows Version 22.0., IBM Corp., Armonk, NY, USA). Analyses were performed on an intention-to treat basis. All *P*-values reported are two-sided; $p < 0.05$ was considered significant.

Results

Patients and hospital controls

The demographic and clinical characteristics of the 20 patients with GBS are given in Table 1. The median age of the patients with GBS was 33 years (range; 18-55); median body weight was 60 kg (IQR, 55-65 kg; range, 50-72 kg) and 13 (65%) patients were male (Fig. 1). On admission and before the start of SVPE, all 20 patients with GBS were unable to walk independently (GBS disability score, 4). One patient required mechanical ventilation from the second day after the onset of weakness; SVPE was started on the fourth day of mechanical ventilation (patient 9, Fig. 1). Two of the 19 patients who did not require mechanical ventilation at the start of the study required mechanical ventilation on the second day after initiation of SVPE (patients 11 and 19, 11 and 2 days after the onset of weakness, respectively; Fig. 1). The median MRC sum score for the limb muscles in all 20 patients was 20 (IQR: 0-29; range: 0-36; Fig. 1). Symptoms of a preceding infection in the 4 weeks before the onset of weakness were present in 18 (90%) patients with GBS, of whom 10 (50%) had diarrhoea. Median duration from admission to start of SVPE was two days (IQR, 2-3 days; range, 0-7 days). Median duration to nadir from the onset of weakness was five days (range, 1-13 days). Electrodiagnostic nerve conduction studies indicated 15 (75%) patients had an axonal subtype and 5 (25%) patients had a demyelinating subtype of GBS. Median duration from onset of weakness to NCS examination was 10 days (range, 4-16 days). All patients had albuminocytologic dissociation; median CSF protein was 166 mg/dL (range 117-253 mg/dL). Median duration from onset of weakness to CSF examination was 11 days (range, 4-17 days).

Median age of the 24 hospital control patients without GBS was 44 years (IQR, 25-57; range; 18-74); 10 (42%) were male. Age and gender distribution were not significantly different compared to the 20 patients with GBS ($p = 0.2155$, $p = 0.1434$, respectively). The diagnoses for these 24

patients were: brain tumour (*n* = 5), transverse myelitis (*n* = 5), head trauma after road traffic accident (*n* = 3), viral meningoencephalitis (*n* = 2), myasthenia gravis (*n* = 2), compressive cervical myelopathy (*n* = 2), cerebrovascular accident (*n* = 2), motor neuron disease (*n* = 1), electrolyte imbalance (*n* = 1) and status epilepticus (*n* = 1).

Primary endpoints

One patient with GBS treated with SVPE developed severe sepsis, possibly due to SVPE-related CLABSI (SVPE window-period blood culture revealed methicillin-resistant *Staphylococcus aureus*). This patient required intravenous fluid, noradrenalin infusion and intravenous antibiotics, but eventually improved (patient 11, Fig. 1). This patient also had signs and symptoms suggestive of aspiration pneumonia and VAP; *Streptococcus spp.* was isolated from pulmonary aspirates. Further laboratory results revealed dys-electrolytemia, anaemia and hypo-albuminemia. No patients experienced deep vein thrombosis due to the CVC for SVPE. Fifteen (75%) of the 20 patients met the primary endpoint of feasibility, defined as the ability to remove at least 8 L of plasma in eight days. The median volume of plasma removed was 8.5 L (IQR, 7.9-8.8 L; range, 6.3-9.6 L; Fig. 1). The median plasma exchange rate was 140 mL/kg bodyweight (IQR, 125-155 mL/kg; range, 110-175 mL/kg) over 8 days and 16 (80%) patients had a plasma exchange rate > 120 mL/kg (Table 2).

Secondary endpoints

Infections among SVPE-treated patients with GBS and hospital controls

Among the 20 patients with GBS treated with SVPE, six (30%) had fever during SVPE (Fig. 1, Supplementary Figure 1), including 2 (10%) patients with leucocytosis who were diagnosed with HAI (VAP and CAUTI in one patient; VAP in one patient). In three out of four (20%) patients with fever without leucocytosis, fever subsided within two to three days without antimicrobial

therapy (Fig. 1). The remaining patient with pyrexia without leucocytosis had microbiological evidence of both CLABSI and VAP (patient 11, Fig. 1). In all other 14 patients with GBS, no fever was documented during the course of SVPE until the tenth day of SVPE (second day after removal of the CVC for SVPE). Five of these 14 patients had leucocytosis, but no site-specific HAI could be detected. However, one of the nine patients without fever but leucocytosis fulfilled the criteria for CAUTI (patient 12, Fig. 1). All three patients who required mechanical ventilation subsequently developed VAP; two of the 13 patients who required a urinary catheter developed a CAUTI (patient 11, Fig. 1). No patients died during the 6 months follow-up.

All 24-hospital control patients without GBS required mechanical ventilation and an indwelling urinary catheter. Of these patients, 22 (92%) patients had fever, of whom 15 (63%) had leucocytosis; a diagnosis of a specific HAI could be made 14 of these 15 patients (CLABSI in two, CAUTI in one, VAP in 11) and four (17%) fulfilled the criteria for severe sepsis (Supplementary Figure 1). Seven (29%) of the 24 hospital control patients had fever without leucocytosis. In two of these seven patients, a specific HAI was diagnosed (CAUTI and VAP in one, and VAP in one). In two hospital control patients, no fever was documented until day 10 after first placement of the CVC, but leucocytosis was present and no site-specific HAI could be detected (Supplementary Figure 1).

The rates of CLABSI, CAUTI and VAP per 1000 device days in the SVPE-treated patients with GBS were 6.25, 19.2 and 40 compared to 10.4, 10.4 and 67.7 for the hospital control patients without GBS, respectively. The relative risks of CLABSI, CAUTI and VAP associated with SVPE were 0.6, 1.2 and 1.8, respectively, compared to hospital control patients. The rates of CLABSI, CAUTI and VAP were comparable between SVPE-treated patients with GBS and hospital control patients ($p > 0.05$). Antimicrobial agents were used more frequently in the

hospital control patients ($p < 0.0001$; Fig. 2). The standardised infection ratios for CLABSI, CAUTI and VAP for SVPE-treated patients with GBS were 0.6, 1.8 and 1.9, respectively.

Other secondary endpoints

Ten (50%) of the 20 patients treated with SVPE experienced transient hypotension during SVPE, which was corrected by infusion of 200-300 mL crystalloid saline (Fig. 1). Minor bleeding through the CVC insertion site (excluding at the time of insertion) was observed in 10/20 patients (50%; Fig. 1); these bleeds required a pressure pack. Reduction of the anticoagulant dose along with a pressure pack was required in 3/20 patients, who all had a prolonged prothrombin time (PT). Three patients had single episode of haemorrhage through the urinary catheter: one was diagnosed with a CAUTI with normal coagulation profile, one had a prolonged PT, the other had sterile haematuria with normal PT. Overall, PT and activated partial thromboplastin time (aPTT) were prolonged in 4/20 patients and only PT was prolonged in 2/20 patients. Clotting time and bleeding time were not prolonged in any patient. One patient developed anaemia (haemoglobin, 8 gm/L) at the end of SVPE; this patient also had severe sepsis and required one unit of blood transfusion (patient 11, Fig. 1). CVC blockages were not observed in any SVPE-treated patients with GBS. One patient with increased clotting tendency who required an increased dose of low molecular weight heparin had shortened clotting time (CT) (< 50% of upper limit of normal), though PT was normal (patient 10, Fig. 1).

The neurological outcomes of the SVPE-treated patients with GBS at six months in terms of neurological scores are given in Table 3. Median time to recover the ability to walk unaided was 4 weeks (Fig. 3). Fourteen (70%) of the 20 patients had an improvement in GBS disability score of one or more grades at four weeks after the onset of SVPE. At one month, 12 patients (60%) were able to walk unaided, two patients (10%) were able to walk aided and six (30%) patients

were bedbound, of whom three still required mechanical ventilation. At three months, 14 (70%) patients were able to walk unaided, one (5%) could walk with aid and five (25%) patients were bedbound. At six months, 14 (70%) patients were able to walk unaided, three (5%) could walk with aid and three (15%) remained bedbound (Table 3).

Other relevant clinical and laboratory findings

Allergic/transfusion reaction to FFP was observed in four patients with GBS treated with SVPE (Fig. 1). These transfusion reactions presented as an itchy erythematous skin rash (three patients), fever (two patients), hypotension (one patient) following transfusion of FFP; all of these reactions were managed with oral antihistamine (and intravenous saline in one patient) without further complications.

The other documented haematological and biochemical abnormalities were hypo-albuminemia (n = 4), thrombocytopenia (n = 6), hyponatraemia (n = 1), hypokalaemia (n = 3), hypomagnesaemia (n = 1), hypocalcaemia (n = 3); (Table 2).

Discussion

Principal findings

This study suggests SVPE may represent a safe and feasible alternative to conventional plasma exchange for patients with severe GBS in limited-resource settings. Of the 20 patients in this study, one (5%) experienced a SAE (severe sepsis due to probable CLABSI). The rate of SAE was not significantly higher than the hospital control group without GBS with a CVC, and no patients had a CVC-related thromboembolic event in patients with SVPE. We were able to remove the prespecified target volume (8 L) of plasma as the target primary endpoint of feasibility in 15/20 (75%) patients with GBS. Median plasma exchange volume and rate during SVPE were 8.4 L and 140 mL/kg, respectively. Minor adverse effects included transient hypotension during SVPE in 50% (10/20), minor haemorrhage from CVC insertion site in 50% (10/20), transfusion reaction to fresh frozen plasma in 20% (4/20), and hypo-albuminemia, anaemia and electrolyte imbalance in 20% (4/20) of patients. An improvement of at least one grade on the GBS disability score was observed for 14/20 (70%) patients at four weeks after the initiation of SVPE. No patients died.

Comparison with baseline hospital control patients and standard PE

With respect to HAIs, no significant differences were observed in the frequency of CLABSI, severe sepsis, VAP or CAUTI between the SVPE-treated patients with GBS and 24 hospital control patients without GBS treated using a CVC in the same ICU or HDU (Fig. 2). However, antimicrobial agents were used more frequently, usually prophylactically, in the hospital control patients compared to the patients with GBS treated with SVPE ($p < 0.0001$; Fig. 2). The probability of detecting microorganisms in clinical infections may have been reduced due to overzealous use of antibiotics in the hospital control patients. Early trials of PE in patients with GBS showed 34% of patients develop severe infections [7, 35]. Subsequently, another large trial

documented septicaemia in 19% of patients [5]. However, the rates of CLABSI were not reported. The volume exchanged during SVPE is within the range recommended in the protocol for standard PE [120-200 mL/kg (standard PE) vs. 140 mL/kg for SVPE] [7]. Exchange of 6 L of plasma in adult patients is clinically beneficial, but less effective than exchange of 12 L; exchanging 18 L provides no added benefit [5]. This suggests that the correlation between clinical benefit and the volume of plasma removed is not linear and exchanging more than 6 L of plasma is likely to have a beneficial effect. We were able to remove >120 mL/kg plasma in 80% of patients, which should provide a therapeutic effect [36]. Notably, the body weight of our patients may be lower than that of patients in western countries. In addition, SVPE was complete within 8 days, shorter than the usual time required for a full session of PE (10 to 12 days).

Important observations in terms of secondary endpoints were transient hypotension, transfusion reaction to FFP and minor bleeding through the CVC insertion site. Hypotension is a common complication during traditional PE that affects nearly half of patients [5]. Spells of hypotension during SVPE were more frequent during the three to four days after initiation of SVPE, and could be easily corrected by rapid infusion of 300-400 mL saline (Fig. 1). The hypotension could possibly be explained by hypovolemia due to drawing blood or as a result of the compromised autonomic nervous system in patients with GBS. As SVPE proceeded, hypotensive spells were encountered less frequently despite drawing the same volume of blood, which may in part be explained by adaptation of the vasomotor system or recovery from autonomic dysfunction. Minor bleeding through the CVC insertion site occurred in 50% of patients and could be controlled by applying a simple pressure pack over the CVC insertion site in most cases; mild prolonged PT was noted in 30% (3/10) patients. However, spontaneous bleeding usually occurs if the PT is more than 2.5 times prolonged and PC is < 0.50 lac/μL [37]. Movement of the limb where the CVC was placed may have caused traction on the CVC and contributed to local bleeding in the other

seven patients. Haematuria is not uncommon in patients with a UTI, as may have occurred in one SVPE treated patient; traumatic traction of the urinary catheter may cause haematuria in two other catheterized SVPE-treated patient taking oral aspirin, who had haematuria and sterile urine. We also monitored the major organ function and biochemical status of the patients treated with SVPE. No patients experienced hepatic or renal impairment. One patient developed anaemia and hypoalbuminemia; this patient had severe sepsis, a common cause of anaemia and hypoalbuminemia in critically ill patients admitted to an ICU (patient 11, Fig. 1). Electrolyte imbalances were detected in 15% of the SVPE-treated patients with GBS, and were mild, subclinical and easily corrected.

The median reported durations to recovery of independent walking in patients with GBS in large-scale RCTs after PE are 53, 52 and 70 days [4, 5, 7]; compared to 30 days in our patients treated with SVPE. Moreover, 60% of the patients with GBS treated with SVPE were able to walk independently at four weeks, whereas 20% of patients with GBS acquired independent walking ability at four weeks after traditional PE [35]. However, these differences may possibly may be due to the small sample size and variations in demographic and neurophysiological characteristics between cohorts. Finally, SVPE was completed in all 20 patients and no patients died.

Limitations of SVPE

SVPE is a time-consuming and labour-intensive procedure, which is a limitation. We used multiple thin-lumen tubing systems interconnected with a multichannel connecter device, which may increase the chance of blood coagulating within the tubing system. Coagulation may require manipulation or replacement of the tubing to ensure free flow of blood and saline. Such handling could increase the chance of microbial contamination. A single continuous wide-lumen tubing system (SVPE kit) could resolve this problem. Most importantly, personnel conducting the SVPE

procedure should maintain proper aseptic technique, which can sometimes be challenging in developing countries. Furthermore, other adaptions such as provision of a larger blood bag or increasing the number of days for SVPE could be considered to increase the plasma exchange rate.

Clinical implications and future research

Despite the limitations, our study showed SVPE is a safe and feasible treatment for GBS in a resource-limited setting where IVIg or PE are either unavailable or unaffordable. Specifically, the poorest 20% of the world's population (1.8 billion people) who typically earn less than 10 US$ per day and who are not covered by a national health insurance system may benefit. Considering the incidence of GBS is 2/100,000 in developing countries, approximately 40,000 patients could potentially benefit from SVPE every year, worldwide. In the future, a multicentre RCT is required to assess the clinical efficacy of SVPE for patients with GBS. If proven effective, SVPE could be an affordable and easily available alternative plasma exchange technique in low-income countries for patients with GBS and other disorders, who at present cannot afford standard PE due to its high cost and unavailability.

Declarations

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Authors' contributions: BI, PVD, BJ, QDM, ZI, and HPE conceived the study design and sample size of the study. MV, MVJ, SR, and HPE contributed to the infection safety guidelines in the study design. BI and QDM conducted the study and BI collected and analysed the data and drafted the manuscript. All authors have critically revised the manuscript and have read and approved the final manuscript.

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Data sharing: The dataset is available from the lead author on request.

Transparency: The corresponding author affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1: Demographic and clinical characteristics of the 20 patients with GBS included in this small volume plasma exchange (SVPE) study at entry

Characteristic		Value
Demography		
Sex [males: females (ratio)]		13:7 (1.85)
Age (years) ¶		33 (18 - 55)
Body weight (kg) ¶		60 (50 -72)
Antecedent events ‡ (total)		18 (90%)
Diarrhoea		10 (50%)
Respiratory infection		5 (25%)
Fever		3 (15%)
Days from antecedent events to weakness ¶		7 (3 - 30)
Days between onset of weakness to admission ¶		7 (2-12)
Neurological deficits at entry		
Weakness in arms and legs		20 (100%)
Cranial nerve deficits		12 (60%)
Decreased deep tendon reflexes		20 (100%)
Sensory involvement		5 (25%)
GBS disability score §	4	19 (95%)
	5	1 (5 %)
Severity of weakness (MRC sum-score) ¶		20 (0-29)
Autonomic dysfunction		11 (55%)

¶ Median (range); † increased protein level (> 45 mg/dL) in combination with CSF cell count < 50/µL; CSF = cerebrospinal fluid; NCS = nerve conduction study; ‡ symptoms of an infection in the four weeks preceding the onset of weakness; § GBS disability score (0 - 6) = 0: healthy state; 1: minor symptoms and capable of running; 2: able to walk 10 meters or more without assistance but unable to run; 3: able to walk 10 meters across an open space with help; 4: bedridden or chair-bound; 5: requiring assisted ventilation for at least part of the day; 6: dead.

Table 2: Treatment characteristics and complications associated with SVPE in the 20 patients with GBS

Characteristic/complication	Value
Treatment characteristics	
Number of sessions of SVPE per patient ¶	30 (24 - 42)
Volume of plasma removed per patient ¶	8.4 (6.3 – 9.6)
Plasma exchange rate (mL/kg) ¶	140 (110-175)
Time between hospital admission and SVPE (days) ¶	8 (5-10)
Time between onset of weakness and start of SVPE (days) ¶	8 (5-10)
Need to stop SVPE due to poor hemodynamic tolerance	0/20 (0%)
Need for blood transfusion for anaemia	1/20 (5%)
Reduction of anticoagulant drug dose for bleeding	3/20 (15%)
Temporary withdrawal of antiplatelet drug for bleeding	4/20 (20%)
Increased anticoagulant drug dose to continue SVPE	1/20 (5%)
CVC blockade/replacement	0/20 (0%)
Complications during SVPE	
Infection	
Leukocytosis	7/20 (35%)
CLABSI §	6.25
VAP §	136.4
CAUTI §	40
Severe sepsis	1/20 (5%)
Antimicrobial agents used	6/20 (30%)
Bleeding and coagulation	
Bleeding from CVC insertion site	10/20 (50%)
Bleeding from mucosal area	3/20 (15%)
Prolonged BT (BT > 10 min)	0/20 (0%)
Prolonged CT (CT > 15 min)	0/20 (0%)
Prolonged PT (PT > 14 sec) ¶	6/20 (30%) [15-19 sec]

Prolonged aPTT (aPTT > 40 sec) ¶	3/20 (15%) [51-240 sec]
Other complications	
Saline responsive hypotension	10/20 (50%)
Anaemia (Hb < 8 gm/L)	2/20 (10%)
Thrombocytopenia (PC < 1.5 lac/µL) ¶	6/20 (30%) [0.79-1.3 lac/µL]
Jaundice (serum bilirubin > 1.2 mg/dL)	0/20 (0%)
Renal impairment (serum creatinin > 1.2 mg/dL)	0/20 (0%)
Hyponatraemia (serum Na^+ < 135 mEq/L)	1/20 (5%) [126 mEq/L]
Hypokalaemia (serum K^+ < 3.5 mEq/L) ¶	3/20 (15%) [2.6-3.2 mEq/L]
Hypoalbuminemia (serum albumin > 35 gm/L) ¶	4/20 (20%) [26-32 gm/L]
Hypocalcaemia (serum Ca^+ < 2.2 mmol/L) ¶	3/20 (15%) [1.89-1.98 mmol/L]
Hypomagnesaemia (serum Mg^+ < 75 mEq/L) ¶	1/20 (5%) [73 mEq/L]
Hypersensitivity/transfusion reaction to FFP	4/20 (20%)

¶ Median (range); § rate per 1000 device days; CLABSI: central line-associated bloodstream infection; VAP: ventilator-associated pneumonia; CAUTI: catheter-associated urinary tract infection; CVC: central venous catheter; BT: bleeding time, CT: clotting time; PT: prothrombin time; APTT: activated partial thromboplastin time; FFP: fresh frozen plasma.

Table 3: Neurological outcomes of the 20 patients with GBS after SVPE

Clinical outcome	1 month	2 months	3 months	6 months
Cranial nerve involvement	7/20 (35%)	6/20 (30%)	4/20 (20%)	2/20 (10%)
Autonomic involvement	3/20 (15%)	3/20 (15%)	0/20 (0%)	0/20 (0%)
Sensory dysfunction	1/20 (5%)	1/20 (5%)	1/20 (5%)	1/20 (5%)
GBS disability score¶	0 = 0	0 = 1	0 = 1	0 = 2
	1 = 3	1 = 6	1 = 7	1 = 7
	2 = 9	2 = 6	2 = 6	2 = 5
	3 = 2	3 = 1	3 = 1	3 = 3
	4 = 3	4 = 5	4 = 5	4 = 3
	5 = 3	5 = 1	5 = 0	5 = 0
MRC sum score † ⁎	47 (0-60)	49 (0-60)	53 (6-60)	58 (22-60)
ONLS ‡ ⁎	4 (1-12)	3 (0-12)	3 (0-12)	2 (0-10)
R-ODS § ⁎	26 (0-41)	33 (0-45)	37 (0-45)	38 (0-46)

⁎ Median (range); ¶ GBS disability score (0 - 6) = 0: healthy state, 1: minor symptoms and capable of running, 2: able to walk 10 meters or more without assistance but unable to run, 3: able to walk 10 meters across an open space with help, 4: bedridden or chair-bound, 5: requiring assisted ventilation for at least part of the day, 6: dead; † MRC sum score: Medical Research Council sum score; ‡ ONLS: Overall Neuropathy Limitation Scale [21]; § R-ODS: Rash-built Overall Disability Score [22]

Figure 1: Feasibility of SVPE and associated complications for the 20 individual patients with GBS.

SVPE: small volume plasma exchange, HAI: hospital acquired infection, V: ventilator-associated pneumonia, B: central line-associated blood stream infection, U: catheter-associated urinary tract infection, [A] measured in litres, ●: spell of hypotension (systolic BP < 90 mm Hg), ◊: CVC insertion site bleeding, ▲: hypersensitivity to fresh frozen plasma, shaded squares: pyrexia due to bacterial infection, dotted squares: pyrexia due to suspected viral infection, M: onset of mechanical ventilation, C: urinary catheterization.

Figure 2: Hospital-acquired infections and use of antibiotics in the 20 patients with GBS receiving SVPE compared to the 24 hospital control patients without GBS treated in an ICU with a CVC who did not receive SVPE.

■ SVPE (n = 20): twenty patients with GBS aged ≥ 18-years-old who were bedbound (GBS disability score ≥ 4) received small volume plasma exchange (SVPE) within 2 weeks of the onset of weakness. ⊡ Non-SVPE (n=20): twenty-four patients aged ≥ 18-years-old with a diagnosis other than GBS who required a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units in the same period as the patients with GBS received SVPE; ∗ $p < 0.0001$.

Figure 3: Kaplan-Meier estimate (with 95% confidence limits) of the cumulative incidence of restoration of independent walking ability in patients with GBS treated with SVPE.

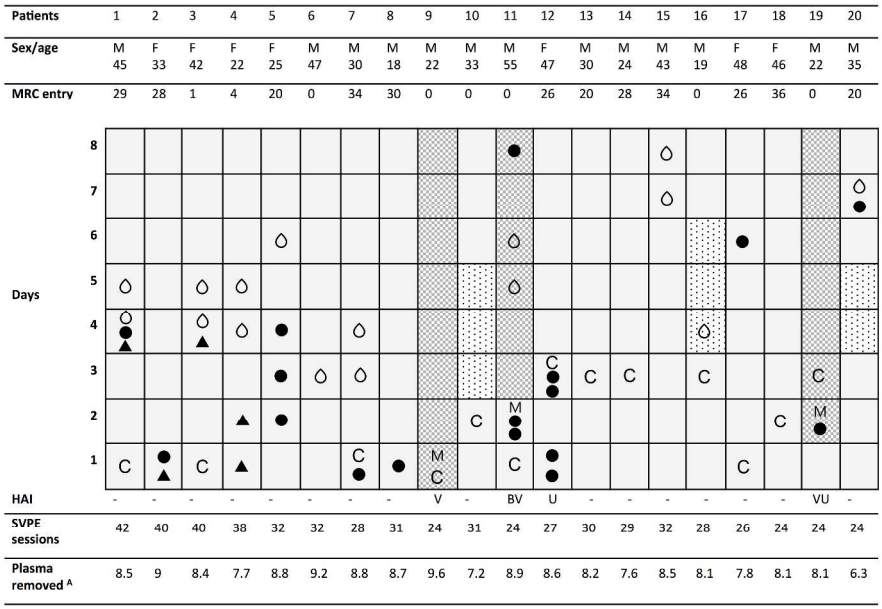
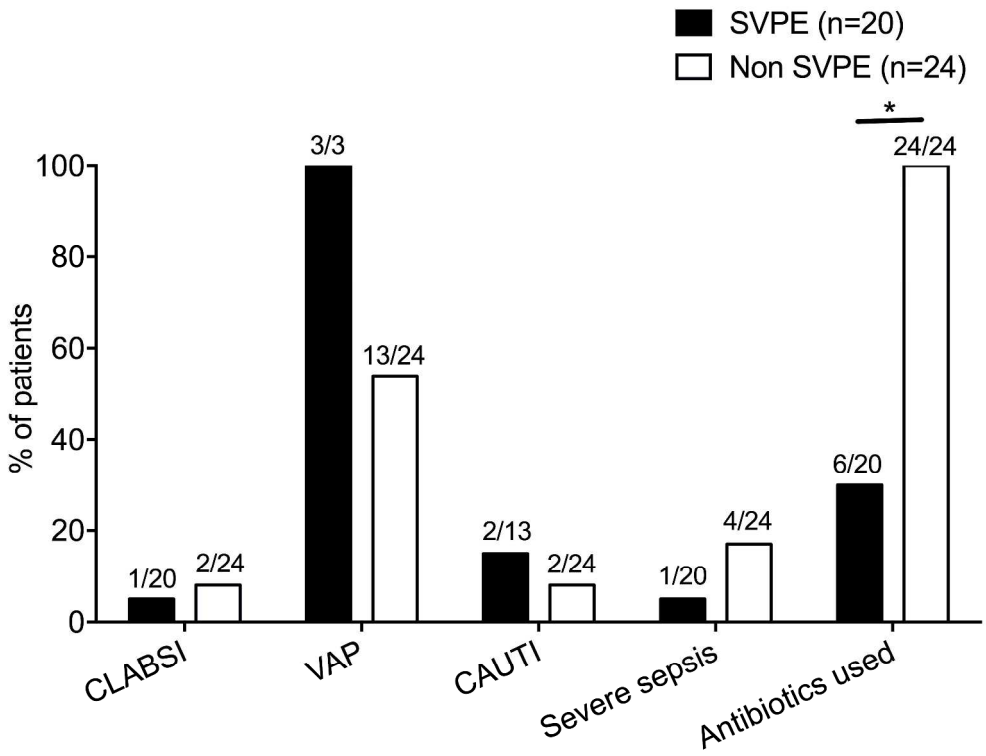


Figure 1: Feasibility of SVPE and associated complications for the 20 individual patients with GBS. SVPE: small volume plasma exchange, HAI: hospital acquired infection, V: ventilator-associated pneumonia, B: central line-associated blood stream infection, U: catheter-associated urinary tract infection, A measured in litres, black dot: spell of hypotension (systolic BP < 90 mm Hg), empty drop: CVC insertion site bleeding, black triangle: hypersensitivity to fresh frozen plasma, shaded squares: pyrexia due to bacterial infection, dotted squares: pyrexia due to suspected viral infection, M: onset of mechanical ventilation, C: urinary catheterization.



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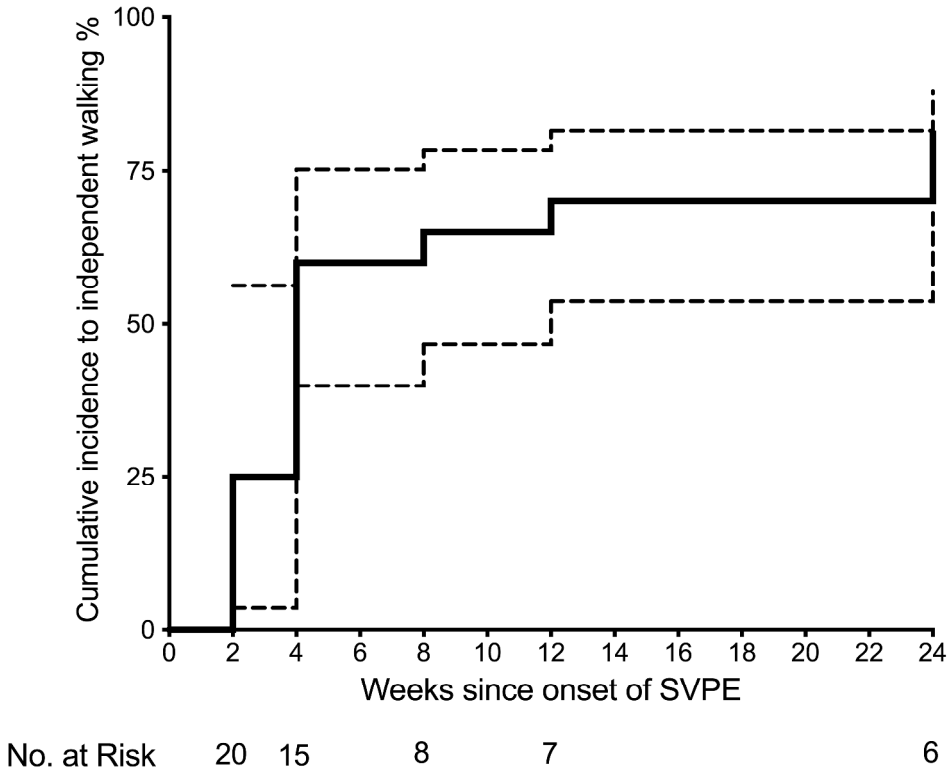
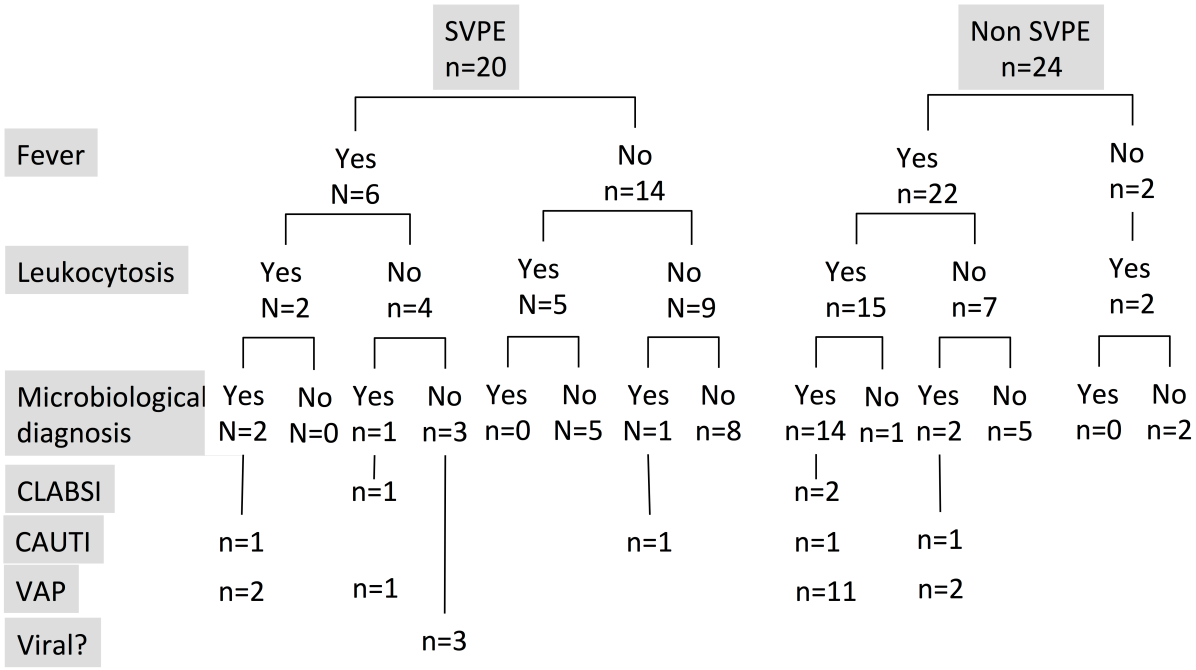


Figure 3: Kaplan-Meier estimate (with 95% confidence limits) of the cumulative incidence of restoration of independent walking ability in patients with GBS treated with SVPE.

Supplementary Figure: Hospital-acquired infections in the 20 patients with GBS treated with SVPE and the 24-hospital control patients without GBS.



SVPE: small volume plasma exchange, CLABSI: central line-associated blood stream infection, CAUTI: catheter-associated urinary tract infection, VAP: ventilator-associated pneumonia.

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Consent form

For a patient's consent to publication of images and/or information about them in BMJ publications.

Name of patient:	**ASHRAF ALI**
Relationship to patient (if patient not signing this form):	**Not applicable**
*Description of the photo, image, text or other material (**Material**) about the patient. **A copy of the Material should be attached to this form**:*	***Video documentation of the small volume plasma exchange (SVPE) procedure***
Provisional title of article in which Material will be included:	**Small volume plasma exchange for Guillain-Barré syndrome in resource-limited settings: a safety and feasibility study**

CONSENT

I_____**ASHRAF ALI (35 years / Male)**_____*[PRINT FULL NAME]* give my consent for the Material about me/the patient to appear in a BMJ publication.

I confirm that I: *(please tick boxes to confirm)*

- ☐ √ ***have seen the video clip about me***
- ☐ √ ***have read the article to be submitted to BMJ***
- ☐ √ ***am legally entitled to give this consent.***

I understand the following:

(1) The Material will be published without my/the patient's name attached, however I understand that complete anonymity cannot be guaranteed. It is possible that somebody somewhere - for example, somebody who looked after me/the patient or a relative - may recognise me/the patient.

(2) The Material may show or include details of my/the patient's medical condition or injury and any prognosis, treatment or surgery that I have/the patient has, had or may have in the future.

(3) The article may be published in a journal which is distributed worldwide. BMJ's publications go mainly to doctors and other healthcare professionals but are also seen by many others including academics, students and journalists.

(4) The article, including the Material, may be the subject of a press release, and may be linked to from social media and/or used in other promotional activities. Once published, the article will be placed on a BMJ website and may also be available on other websites.

(5) The text of the article will be edited for style, grammar and consistency before publication.

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(6) I/the patient will not receive any financial benefit from publication of the article.

(7) The article may also be used in full or in part in other publications and products published by BMJ and/or by other publishers. This includes publication in English and in translation, in print, in digital formats, and in any other formats that may be used by BMJ or other publishers now and in the future. The article may appear in local editions of journals or other publications, published in the UK and overseas.

(8) I can revoke my consent at any time before publication, but once the article has been committed to publication ("gone to press") it will not be possible to revoke the consent.

(9) This consent form will be retained securely and in confidence by BMJ in accordance with the law, for no longer than necessary.

Please tick boxes to confirm the following:

☐ √ I consent to BMJ storing my contact details (including outside of the EEA) for the sole purpose of contacting me, if necessary, in the future.

☐ Where this consent relates to an article in *BMJ Case Reports*, I have/the patient has had the opportunity to comment on the article and I am satisfied that the comments, if any, have been reflected in the article.

Signed: ASHRAF ALI' *Print name:* **ASHRAF ALI**

Address:
House: 4; Road: 2/1; Rupnagar R/A; Mirpur-1;
Dhaka;
Bangladesh

Email address: **ashrafali3972@gmail.com**

Telephone no: **+880 17 1201 0384**

If signing on behalf of the patient, please give the reason why the patient can't consent for themselves (e.g. patient is deceased, under 18 or has cognitive or intellectual impairment). ***Not applicable***

Date: **16. 02. 2018**

☐ *If you are signing for a family or other group, please tick the box to confirm that all relevant members of the family or group have been informed.* ***Not applicable***

If the patient is a child aged 7 years or older, they must also confirm their consent: ***Not applicable***

Signed: _____ *Print name:* _____

Date of birth: _____ *Date:* _____

Patient consent form 031117

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Details of person who has explained and administered the form to the patient or their representative (e.g. the corresponding author or other person who has the authority to obtain consent).

Signed:

Print name: **Dr Md Badrul Islam**

Position:

Research Trainee and PhD Fellow

Institution:

International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b)

Address:

Laboratory Sciences and Services Division (LSSD)

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Date: **16. 02. 2018**

2017 CONSORT checklist of information to include when reporting a randomized trial assessing nonpharmacologic treatments (NPTs)*. Modifications of the extension appear in italics and blue.

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
Title and abstract					
	1a	Identification as a randomized trial in the title	NA (Non-randomized)		
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3, 4, 5	Refer to CONSORT extension for abstracts for NPT trials	3, 4, 5
Introduction					
Background and objectives	2a	Scientific background and explanation of rationale	6		
	2b	Specific objectives or hypotheses	6, 7		
Methods					
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7	When applicable, how care providers were allocated to each trial group	NA
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	No changes to methods after trial commencement		
Participants	4a	Eligibility criteria for participants	7, 8	When applicable, eligibility criteria for centers and for care providers	NA
	4b	Settings and locations where the data were collected	7		
Interventions†	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7, 8	Precise details of both the experimental treatment and comparator	7, 8
	5a			Description of the different components of the interventions and, when applicable, description of the procedure for tailoring the interventions to individual participants.	9
	5b			Details of whether and how the interventions were standardized.	8, 9

Cite as: *Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40–7.*

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
	5c.			Details of whether and how adherence of care providers to the protocol was assessed or enhanced	8, 9
	5d			Details of whether and how adherence of participants to interventions was assessed or enhanced	NA
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8, 9		
	6b	Any changes to trial outcomes after the trial commenced, with reasons	No changes to trial outcomes after the trial commenced		
Sample size	7a	How sample size was determined	9	When applicable, details of whether and how the clustering by care providers or centers was addressed	NA
	7b	When applicable, explanation of any interim analyses and stopping guidelines	10		
Randomization:					
- Sequence generation	8a	Method used to generate the random allocation sequence	NA (Non-randomized)		
	8b	Type of randomization; details of any restriction (such as blocking and block size)	NA (Non-randomized)		
- Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	NA (Non-randomized)		
- Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	NA (Non-randomized)		
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Blinding was not possible	If done, who was blinded after assignment to interventions (e.g., participants, care providers, those administering co-interventions, those assessing outcomes) and how	Blinding was not possible

Cite as: *Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40–7.*

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
	11b	If relevant, description of the similarity of interventions	7, 8		
	11c			If blinding was not possible, description of any attempts to limit bias	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10	When applicable, details of whether and how the clustering by care providers or centers was addressed	NA
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NA		
Results					
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	11	The number of care providers or centers performing the intervention in each group and the number of patients treated by each care provider or in each center	Single center study
	13b	For each group, losses and exclusions after randomization, together with reasons	No losses and exclusions after inclusion		
	13c			For each group, the delay between randomization and the initiation of the intervention	11
	new			Details of the experimental treatment and comparator as they were implemented	11, 12, 13, 14
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7		
	14b	Why the trial ended or was stopped	NA (Trial completed)		
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1	When applicable, a description of care providers (case volume, qualification, expertise, etc.) and centers (volume) in each group.	NA
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11		

Cite as: *Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40–7.*

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12, 13, 14		
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA		
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	15		
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12, 13, 14, 15		
Discussion					
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	18, 19	In addition, take into account the choice of the comparator, lack of or partial blinding, and unequal expertise of care providers or centers in each group	NA
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	16, 17, 18	Generalizability (external validity) of the trial findings according to the intervention, comparators, patients, and care providers and centers involved in the trial	16, 17, 18
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16, 17, 18		
Other information					
Registration	23	Registration number and name of trial registry	4		
Protocol	24	Where the full trial protocol can be accessed, if available	Manuscript reference no: 16		
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	20		

**Additions or modifications to the 2010 CONSORT checklist. CONSORT = Consolidated Standards of Reporting Trials*
†The items 5, 5a, 5b, 5c, 5d are consistent with the Template for Intervention Description and Replication (TIDieR) checklist

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Table: Required documents of the safety and feasibility study of the small volume plasma exchange (SVPE) for Guillain-Barré syndrome patients for the World Health Organization Trial Registration Data Set

	Item/Label	Description
1	Primary Registry and Trial **Identifying** Number	Clinicaltrials.gov NCT02780570
2	Date of Registration in Primary Registry	May 23, 2016
3	Secondary Identifying Numbers	International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) Protocol Number: PR-15086, Version no. 3, Date: 09/12/2015
4	Source(s) of Monetary or Material Support	GBS/CIDP Foundation International Fondation Mérieux: (Small Grants Program 2015)
5	Primary Sponsor	GBS/CIDP Foundation International
6	Secondary Sponsor(s)	Fondation Mérieux: (Small Grants Program 2014)
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9	Public title	Small volume plasma exchange for Guillain-Barré syndrome
10	Scientific title	Small volume plasma exchange for Guillain-Barré syndrome in low-income countries: a safety and feasibility study
11	Countries of Recruitment	Bangladesh
12	Health condition(s) or problem(s) studied	Guillain-Barré syndrome (GBS)
13	Interventions	*Small Volume Plasma Exchange (SVPE)* A loading dose of low-molecular weight heparin (1.5 mg/kg) will be given subcutaneously at least two hours

before initiation of SVPE; the same dose will be administered once daily or divided into two equal doses daily for eight days or until SVPE is completed. Whole blood (7 mL/kg body weight) will be drawn from the central venous catheter into the blood transfusion bag in each session. The blood bag will be hung beside the patient for 2.5 h on a saline stand and left uninterrupted to allow plasma and blood cells to separate. The blood cells will be infused back into the patient and plasma will be discarded and replaced with fresh frozen plasma and colloid solution alternately (in equal volumes) via the closed-circuit SVPE kit illustrated in. In case of excessive clotting (bleeding time reduction of > 50% of baseline for that patient), aspirin (600 mg) will be administered orally at least two hours before the next SVPE session and continued thereafter at 150 mg orally/day until SVPE is completed. One blood bag will be used each day, with a total of six sessions/day. A total of 48 sessions will be performed over eight days, removing approximately 8000 mL plasma in total.

Central venous catheterized patients without GBS

To compare the safety of SVPE in patients with GBS in the context of the background risk of central line-associated blood stream infection (CLABSI) at the study intensive care (ICU) and high-dependency care (HDU) units, the incidence of CLABSI will be assessed in a control group of adult patients with a diagnosis other than GBS admitted to the same ICU and HDU units in the same period of time the patients with GBS will be enrolled for SVPE. We will assess the rate of CLABSI in

		patients aged ≥ 18-years-old requiring a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units.
14	Key Inclusion and Exclusion Criteria	*Inclusion criteria for SVPE in GBS patients* 1. Patients aged ≥ 18-years-old fulfilling the diagnostic criteria for GBS of the National Institute of Neurological and Communicative Disorders and Stroke (NINDS) 2. Unable to walk unaided for more than 10 meters (GBS disability score ≥ 3) 3. Presented within 2 weeks of the onset of weakness 4. Unable to afford standard treatment with IVIg or PE. *Exclusion criteria for SVPE in GBS patients* 1. Patients with severe or terminal concomitant illness 2. Evidence of healthcare-associated infection on admission (except for aspiration pneumonia) 3. Previous history of severe allergic reaction to properly matched blood products and pregnant women will be excluded from the study. *Inclusion criteria for patients without GBS* 1. Patients aged ≥ 18-years-old 2. Requiring a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units in the same period of time the patients with GBS enrolled for SVPE. *Exclusion criteria for patients without GBS*

		1. Patients with healthcare-associated infection present on admission (except aspiration pneumonia) 2. Pregnant women
15	Study type	*Type of the study*: Interventional *Method of allocation:* Non-randomized *Masking:* Non-masked *Assignment:* Parallel arm • SVPE in patients with GBS • Rate of CLABSI in patients without GBS *Purpose:* Safety and feasibility of SVPE
16	Date of first enrolment	February 20, 2016
17	Target sample size	SVPE in patients with GBS = 20 Rate of CLABSI in patients without GBS = ≥ 20
18	Recruitment status	Completed: • Twenty cases of GBS have been successfully treated with SVPE and 24 control cases without GBS have been recruited.
19	Primary Outcome(s)	*Primary outcome of safety*: 1. Number of patients with GBS treated with SVPE developing severe sepsis or septic shock due to central line associated blood stream infection (CLABSI) as per standard guideline (Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central line-associated Bloodstream Infection); CDC Device-associated Module, BSI. January 2017) 2. Occurrence of venous thrombosis in the limb

		where the CVC is placed. Venous thrombosis will be assessed according to Wells criteria (*Philip S. Wells et al. Evaluation of d -Dimer in the Diagnosis of Suspected Deep-Vein Thrombosis; N Engl J Med 2003;349:1227-35*) *Primary outcome of feasibility*: 1. Ability to remove at least eight litres of plasma by SVPE over eight days.
20	Secondary Outcome(s)	*Secondary outcome of safety*: 2. Relative risk of CLABSI due to SVPE compared to CLABSI in control patients without GBS treated using a CVC 3. Hemodynamic instability during the SVPE procedure (variations in systolic blood pressure greater than 30 mmHg or sudden bradycardia involving a reduction in heart rate by more than 20 beats per min within 30 min of starting SVPE or an increase in heart rate above 120 beats per min) 4. Development of anaemia (Hb <7 gm/dL) or serious haemorrhage requiring blood transfusion. *Secondary outcome of feasibility*: 1. Rate of CVC occlusion during the SVPE procedure 2. The healthcare personnel's acceptability and

		satisfaction with the SVPE procedure and any unanticipated events compromising the SVPE procedure as assessed using a standard questionnaire. 3. Neurological outcome will be assessed in terms of improvement in GBS disability score and MRC sum score at discharge and up to 4 weeks after entry.

BMJ Open

Small volume plasma exchange for Guillain-Barré syndrome in resource-limited settings: a phase II safety and feasibility study

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Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.

SUPPLEMENTARY VIDEO.mp4

Title:

Small volume plasma exchange for Guillain-Barré syndrome in resource-limited settings: a phase II safety and feasibility study

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ABSTRACT

OBJECTIVE

To assess the safety and feasibility of small volume plasma exchange (SVPE) as an alternative to standard plasma exchange (PE) or intravenous immunoglobulin (IVIg) for Guillain-Barré syndrome (GBS) patients.

DESIGN

Non-randomized, single arm, interventional trial.

SETTING

National Institute of Neurosciences and Hospital, Dhaka, Bangladesh.

PARTICIPANTS

Twenty adult (>18 years) patients with GBS presented within 2 weeks of onset of weakness who were unable to walk unaided for more than 10 meters.

INTERVENTIONS

SVPE involves blood cell sedimentation in a blood bag and removal of supernatant plasma after blood cells are re-transfused. This procedure was repeated three to six times a day, for eight consecutive days.

OUTCOME MEASURES

Serious adverse events (SAE) were defined as severe sepsis and deep venous thrombosis related to the central vein catheter (CVC) used during SVPE. SVPE was considered safe if less than 5/20 patients experienced a SAE, and feasible if 8 L plasma could be removed within 8 days in at least 15/20 patients.

RESULTS

Median patient age 33 years (IQR 23-46; range 18-55); 13 (65%) were male. Median MRC sum score was 20 (IQR 0-29; range 0-36); three (15%) patients required mechanical ventilation. One patient developed SAE (severe sepsis, possibly related to CVC). Minor adverse effects were

transient hypotension in 10 (50%) patients; CVC-associated bleeding in 10 (50%); transfusion reaction to fresh frozen plasma in 4 (20%); and hypo-albuminemia, anaemia or electrolyte imbalance in 4 (20%). Removal of 8 L plasma was possible in 15 (75%) patients. GBS disability score improved by at least one grade in 14 (70%) patients four weeks after SVPE started. No patients died.

CONCLUSION

SVPE seems a safe and feasible alternative treatment to standard PE or IVIg for GBS; further studies of clinical efficacy in low-resource developing countries are warranted.

TRIAL REGISTRATION

Clinicaltrials.gov NCT02780570 on May 23, 2016

Strength and limitations of the study:

1. The strength of this study underlies the novel and simple technique of SVPE, which is much less expensive than conventional immunotherapies (plasma exchange and intravenous immunoglobulin)
2. SVPE is corroborated as safe and feasible for the first time in a prospective and standardized cohort of patients with Guillain-Barré syndrome (GBS).
3. The intrinsic limitations of this study are its non-randomized, single arm nature, which is conducted in a single center with a limited sample size of GBS patients.
4. Clinical efficacy of SVPE on patients with GBS was a secondary end-point assessment and therefore deserves a randomized controlled trial in future to assess the clinical efficacy of SVPE for the patients with GBS.

Introduction

Guillain-Barré syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy with a yearly incidence of 1.2 to 2.3 cases per 100,000 per year.[1] GBS is characterized by rapidly progressive limb weakness and, in a proportion of cases, respiratory failure (25%) or severe autonomic dysfunction (10%). Plasma exchange (PE) was the first treatment proven to be effective for GBS, if given within 4 weeks of the onset of weakness.[2-10] Conventionally for GBS patients, three to six plasma exchange sessions are done in alternate days targeting removal of nearly 12 litres of patient plasma (approximately 3 litres of plasma at each session) within a span of 9 to 14 days.[11] This give rise to the plasma exchange rate of 120 - 200 ml/kg (40-50ml/kg/day). Later studies showed treatment with intravenous immunoglobulin (IVIg) (0.4 g/kg per day for 5 days) has a similar efficacy as PE in patients with GBS who are unable to walk, if started within 2 weeks of the onset of weakness.[12 13]

Unfortunately, most patients in low-income countries cannot afford expensive treatment with either PE or IVIg.[14] In Bangladesh, a full course of IVIg for a 60 kg adult costs approximately 12,000-16,000 US$ and treatment with conventional PE for 5 days costs approximately 4,500-5,000 US$. The mean income in Bangladesh was 4 US$ per day in 2016 (World Bank and Bangladesh Bureau of Statistics 2016); IVIg and PE cost the equivalent of 3,000 and 1,250 mean income days, respectively. At present, the majority (92%) of patients with GBS in Bangladesh receive supportive care only.[14] In addition, mobile PE equipment is not available in Bangladesh; therefore, patients admitted to the intensive care unit (ICU) cannot receive PE. We previously reported the mortality rates for GBS in Bangladesh range from 12 to 14% and observed 29% of patients with GBS in Bangladesh are unable to walk at 6 months after onset; these poor outcomes are undoubtedly due to the low rates of specific treatment with PE or IVIg.[15 16]

Small volume plasma exchange (SVPE) may represent a cheap, effective alternative treatment for GBS. SVPE is based on the same principle as conventional PE (selective removal of plasma) but uses a novel, simple technique with much lower costs (approximately 500 US$). The current non-randomized trial was designed to investigate the safety and feasibility of SVPE in 20 patients with GBS admitted to the National Institute of Neurosciences Hospital in Dhaka, Bangladesh.

Methods/Design

Study design

For this non-randomized, single arm, interventional safety and feasibility trial, 20 adult patients with GBS were enrolled between March 2016 and December 2016 for SVPE at the National Institute of Neurosciences and Hospital (NINS), Dhaka, Bangladesh. A detailed study protocol was published previously and includes definitions of all variables used in this study.[17]

Four to six daily sessions of whole blood sedimentation and removal of supernatant plasma after re-transfusion of the sedimented blood cells was planned for the 20 patients with GBS, with a target of removing an overall volume of at least 8 litres (L) of plasma over a total of 8 days.[17] (See supplementary video for SVPE procedure)

Patients with GBS were monitored according to a standard protocol throughout the course of SVPE until the second day after withdrawal of the central venous catheter (CVC) in order to assess predefined measures of safety and feasibility and followed up for six months to assess neurological outcome. The protocol was reviewed and approved by the institutional research and ethics review committees at the icddr,b and registered at clinicaltrials.gov (NCT02780570).[17] All patients provided written informed consent to participate in this study.

Patient and Public Involvement

Patients and or public were not involved either in the development of the research question, study design and outcome measure or recruitment to and conduct of the study.

Inclusion and exclusion criteria for patients with GBS

Patients aged ≥ 18-years-old fulfilling the diagnostic criteria for GBS of the National Institute of Neurological and Communicative Disorders and Stroke (NINDS)[18] were enrolled, provided they were unable to walk unaided for more than 10 meters (GBS disability score ≥ 3), presented within 2 weeks of the onset of weakness, and were unable to afford standard treatment with IVIg or PE. Patients with concomitant severe or terminal illnesses, evidence of healthcare-associated infection (HAI) on admission (except for aspiration pneumonia), a previous history of severe allergic reactions to properly matched blood products, and pregnant women were excluded from the study.

Control cohort

To compare the safety of SVPE in patients with GBS in the context of the background risk of central line-associated blood stream infection (CLABSI) at our institution, we prospectively assessed the incidence of CLABSI in a hospital control group of 24 adult patients without GBS receiving neurocritical care. Hospital controls were eligible based on the following characteristics: ≥ 18-years-old, a neurological diagnosis other than GBS, and a CVC placed for > 2 and ≤ 8 calendar days after admission to the same ICU or HDU unit as the SVPE-treated patients. Patients with a HAI (except aspiration pneumonia) and pregnant women were excluded from the control group.

Primary and secondary outcome measures

The primary outcome measures of safety were the number of patients with GBS treated with SVPE who developed either severe sepsis or septic shock due to CLABSI[19] and the occurrence of venous thrombosis in the limb where the CVC was placed. The primary outcome measure of feasibility was the ability to remove at least 8 L of plasma over 8 days.

The secondary outcome measures of the safety of SVPE were the relative risk of CLABSI due to SVPE (compared to CLABSI in the hospital control group without GBS), hemodynamic instability during the SVPE procedure, and development of anaemia (Hb < 8 gm/dL) or any catheter-related haemorrhage requiring a blood transfusion.

The secondary outcome measure of feasibility of SVPE was the rate of CVC occlusion during the SVPE procedure. In addition, neurological outcome was assessed using the GBS disability score[20], MRC sum score[21], Overall Neuropathy Limitation Scale (ONLS)[22] and Rasch-built Overall Disability Scale (R-ODS)[23] at 1st, 2nd , 3rd , and 6th months from the start of SVPE.

Procedure safety and documentation

Strict aseptic procedures were followed to prevent CLABSI.[24-26] SVPE was documented in terms of the duration and amount of plasma removed in each session, and the type and volume of replacement fluid and fresh frozen plasma (FFP) used. Throughout the procedure, the haemodynamic, haematological, biochemical, coagulation and infection profiles of the SVPE-treated patients were monitored according to the protocol.[17] Screening for hepatitis B and C viruses, human immunodeficiency virus (HIV) and syphilis were performed as patient baseline assessments, and also on donor FFP before administration. CLABSI, primary and secondary bloodstream infections[19], catheter-associated urinary tract infection (CAUTI)[27], ventilator-associated pneumonia (VAP)[28] and other HAI[29 30] were documented in the SVPE-treated patients with GBS and the hospital control group.

Sample size

This safety and feasibility study enrolled 20 patients with GBS for SVPE. We could not perform a formal power calculation for this safety and feasibility study. The sample size was based on previous pilot studies conducted in GBS.[31 32] The baseline rate of CLABSI was measured in the hospital control group of 24 patients without GBS admitted to the same study facility who required a CVC for at least 8 days during the study period.

Stopping rules for the trial based on safety and feasibility

Decision to stop the SVPE trial was designated using a Bayesian approach.[33-35] Accordingly, a predictive success rate of 75% was predefined for the SVPE procedure. If more than 5 of 20 patients experienced an SAE, or if it appeared impossible to remove at least 8 L of plasma over 8 days in at least 15 of 20 patients, the procedure was considered unsafe or unfeasible.

Statistical analysis

The rate of HAIs (CLABSI, VAP and CAUTI) per 1000 device days were calculated by dividing the number of each HAI during the study period by the number of device days and multiplying the result by 1000. The infection safety profile for SVPE was assessed by calculating the standardized infection ratio to define the risk of HAIs in patients with GBS treated with SVPE. The standardised infection ratio (SIR) was calculated by dividing the number of observed HAI by the number of HAI predicted (i.e., the infection rate in the control group). The predicted HAI rate was calculated using the rates of HAI in the hospital control group of patients without GBS during the study period. Percentage values were compared using the Chi-square test or Fisher's exact test (two-tailed) and median values, the Mann-Whitney U-test using SPSS 22 software (IBM SPSS Statistics for Windows Version 22.0., IBM Corp.,

Armonk, NY, USA). Analyses were performed on an intention-to treat basis. All *P*-values reported are two-sided; $p < 0.05$ was considered significant.

Results

Patients and hospital controls

The demographic and clinical characteristics of the 20 patients with GBS are given in Table 1. The median age of the patients with GBS was 33 years (range; 18-55); median body weight was 60 kg (IQR, 55-65 kg; range, 50-72 kg) and 13 (65%) patients were male (Fig. 1). On admission and before the start of SVPE, all 20 patients with GBS were unable to walk independently (GBS disability score, 4). One patient required mechanical ventilation from the second day after the onset of weakness; SVPE was started on the fourth day of mechanical ventilation (patient 9, Fig. 1). Two of the 19 patients who did not require mechanical ventilation at the start of the study required mechanical ventilation on the second day after initiation of SVPE (patients 11 and 19, 11 and 2 days after the onset of weakness, respectively; Fig. 1). The median MRC sum score for the limb muscles in all 20 patients was 20 (IQR: 0-29; range: 0-36; Fig. 1). Symptoms of a preceding infection in the 4 weeks before the onset of weakness were present in 18 (90%) patients with GBS, of whom 10 (50%) had diarrhoea. Median duration from admission to start of SVPE was two days (IQR, 2-3 days; range, 0-7 days). Median duration to nadir from the onset of weakness was five days (range, 1-13 days). Electrodiagnostic nerve conduction studies indicated 15 (75%) patients had an axonal subtype and 5 (25%) patients had a demyelinating subtype of GBS. Median duration from onset of weakness to NCS examination was 10 days (range, 4-16 days). All patients had albuminocytologic dissociation; median CSF protein was 166 mg/dL (range 117-253 mg/dL). Median duration from onset of weakness to CSF examination was 11 days (range, 4-17 days).

Median age of the 24 hospital control patients without GBS was 44 years (IQR, 25-57; range; 18-74); 10 (42%) were male. Age and gender distribution were not significantly different compared to the 20 patients with GBS ($p = 0.2155$, $p = 0.1434$, respectively). The diagnoses for these 24 patients were: brain tumour ($n = 5$), transverse myelitis ($n = 5$), head trauma after road traffic accident ($n = 3$), viral meningoencephalitis ($n = 2$), myasthenia gravis ($n = 2$), compressive cervical myelopathy ($n = 2$), cerebrovascular accident ($n = 2$), motor neuron disease ($n = 1$), electrolyte imbalance ($n = 1$) and status epilepticus ($n = 1$).

Primary endpoints

One patient with GBS treated with SVPE developed severe sepsis, possibly due to SVPE-related CLABSI (SVPE window-period blood culture revealed methicillin-resistant *Staphylococcus aureus*). This patient required intravenous fluid, noradrenalin infusion and intravenous antibiotics, but eventually improved (patient 11, Fig. 1). This patient also had signs and symptoms suggestive of aspiration pneumonia and VAP; *Streptococcus spp.* was isolated from pulmonary aspirates. Further laboratory results revealed dys-electrolytemia, anaemia and hypo-albuminemia. No patients experienced deep vein thrombosis due to the CVC for SVPE. Fifteen (75%) of the 20 patients met the primary endpoint of feasibility, defined as the ability to remove at least 8 L of plasma in eight days. The median volume of plasma removed was 8.5 L (IQR, 7.9-8.8 L; range, 6.3-9.6 L; Fig. 1). The median plasma exchange rate was 140 mL/kg bodyweight (IQR, 125-155 mL/kg; range, 110-175 mL/kg) over 8 days and 16 (80%) patients had a plasma exchange rate > 120 mL/kg (Table 2).

Secondary endpoints

Infections among SVPE-treated patients with GBS and hospital controls

Among the 20 patients with GBS treated with SVPE, six (30%) had fever during SVPE (Fig. 1, Supplementary Figure 1), including 2 (10%) patients with leucocytosis who were diagnosed with HAI (VAP and CAUTI in one patient; VAP in one patient). In three out of four (20%) patients with fever without leucocytosis, fever subsided within two to three days without antimicrobial therapy (Fig. 1). The remaining patient with pyrexia without leucocytosis had microbiological evidence of both CLABSI and VAP (patient 11, Fig. 1). In all other 14 patients with GBS, no fever was documented during the course of SVPE until the tenth day of SVPE (second day after removal of the CVC for SVPE). Five of these 14 patients had leucocytosis, but no site-specific HAI could be detected. However, one of the nine patients without fever but leucocytosis fulfilled the criteria for CAUTI (patient 12, Fig. 1). All three patients who required mechanical ventilation subsequently developed VAP; two of the 13 patients who required a urinary catheter developed a CAUTI (patient 11, Fig. 1). No patients died during the 6 months follow-up.

All 24-hospital control patients without GBS required mechanical ventilation and an indwelling urinary catheter. Of these patients, 22 (92%) patients had fever, of whom 15 (63%) had leucocytosis; a diagnosis of a specific HAI could be made 14 of these 15 patients (CLABSI in two, CAUTI in one, VAP in 11) and four (17%) fulfilled the criteria for severe sepsis (Supplementary Figure 1). Seven (29%) of the 24 hospital control patients had fever without leucocytosis. In two of these seven patients, a specific HAI was diagnosed (CAUTI and VAP in one, and VAP in one). In two hospital control patients, no fever was documented until day 10 after first placement of the CVC, but leucocytosis was present and no site-specific HAI could be detected (Supplementary Figure 1).

The rates of CLABSI, CAUTI and VAP per 1000 device days in the SVPE-treated patients with GBS were 6.25, 19.2 and 40 compared to 10.4, 10.4 and 67.7 for the hospital control patients without GBS, respectively. The relative risks of CLABSI, CAUTI and VAP associated with SVPE were 0.6, 1.2 and 1.8, respectively, compared to hospital control patients. The rates of CLABSI, CAUTI and VAP were comparable between SVPE-treated patients with GBS and hospital control patients ($p > 0.05$). Antimicrobial agents were used more frequently in the hospital control patients ($p < 0.0001$; Fig. 2). The standardised infection ratios for CLABSI, CAUTI and VAP for SVPE-treated patients with GBS were 0.6, 1.8 and 1.9, respectively.

Other secondary endpoints

Ten (50%) of the 20 patients treated with SVPE experienced transient hypotension during SVPE, which was corrected by infusion of 200-300 mL crystalloid saline (Fig. 1). Minor bleeding through the CVC insertion site (excluding at the time of insertion) was observed in 10/20 patients (50%; Fig. 1); these bleeds required a pressure pack. Reduction of the anticoagulant dose along with a pressure pack was required in 3/20 patients, who all had a prolonged prothrombin time (PT). Three patients had single episode of haemorrhage through the urinary catheter: one was diagnosed with a CAUTI with normal coagulation profile, one had a prolonged PT, the other had sterile haematuria with normal PT. Overall, PT and activated partial thromboplastin time (aPTT) were prolonged in 4/20 patients and only PT was prolonged in 2/20 patients. Clotting time and bleeding time were not prolonged in any patient. One patient developed anaemia (haemoglobin, 8 gm/L) at the end of SVPE; this patient also had severe sepsis and required one unit of blood transfusion (patient 11, Fig. 1). CVC blockages were not observed in any SVPE-treated patients with GBS. One patient with increased clotting tendency who required an increased dose of low molecular weight heparin had shortened clotting time (CT) (< 50% of upper limit of normal), though PT was normal (patient 10, Fig. 1).

The neurological outcomes of the SVPE-treated patients with GBS at six months in terms of neurological scores are given in Table 3. Median time to recover the ability to walk unaided was 4 weeks (Fig. 3). Fourteen (70%) of the 20 patients had an improvement in GBS disability score of one or more grades at four weeks after the onset of SVPE. At one month, 12 patients (60%) were able to walk unaided, two patients (10%) were able to walk aided and six (30%) patients were bedbound, of whom three still required mechanical ventilation. At three months, 14 (70%) patients were able to walk unaided, one (5%) could walk with aid and five (25%) patients were bedbound. At six months, 14 (70%) patients were able to walk unaided, three (5%) could walk with aid and three (15%) remained bedbound (Table 3).

Other relevant clinical and laboratory findings

Allergic/transfusion reaction to FFP was observed in four patients with GBS treated with SVPE (Fig. 1). These transfusion reactions presented as an itchy erythematous skin rash (three patients), fever (two patients), hypotension (one patient) following transfusion of FFP; all of these reactions were managed with oral antihistamine (and intravenous saline in one patient) without further complications.

The other documented haematological and biochemical abnormalities were hypo-albuminemia (n = 4), thrombocytopenia (n = 6), hyponatraemia (n = 1), hypokalaemia (n = 3), hypomagnesaemia (n = 1), hypocalcaemia (n = 3); (Table 2).

Immunoglobulin dosage admitted by FFP

During SVPE the median volume of FFP received per GBS patient as replacement fluid was 6000 ml (range, 5000 ml to 6000 ml). Considering the normal plasma IgG level of 11.20 mg/ml

(range, 6.9 mg – 17.6 mg)[36], SVPE treated GBS patients received IgG dose of median 0.9 g/kg (range 0.6 g/kg – 1.3 g/kg).

Discussion

Principal findings

This study suggests SVPE may represent a safe and feasible alternative to conventional plasma exchange for patients with severe GBS in limited-resource settings. Of the 20 patients in this study, one (5%) experienced a SAE (severe sepsis due to probable CLABSI). The rate of SAE was not significantly higher than the hospital control group without GBS with a CVC, and no patients had a CVC-related thromboembolic event in patients with SVPE. We were able to remove the prespecified target volume (8 L) of plasma as the target primary endpoint of feasibility in 15/20 (75%) patients with GBS. Median plasma exchange volume and rate during SVPE were 8.4 L and 140 mL/kg, respectively. Minor adverse effects included transient hypotension during SVPE in 50% (10/20), minor haemorrhage from CVC insertion site in 50% (10/20), transfusion reaction to fresh frozen plasma in 20% (4/20), and hypo-albuminemia, anaemia and electrolyte imbalance in 20% (4/20) of patients. An improvement of at least one grade on the GBS disability score was observed for 14/20 (70%) patients at four weeks after the initiation of SVPE. No patients died.

Comparison with baseline hospital control patients and standard/modified PE

With respect to HAIs, no significant differences were observed in the frequency of CLABSI, severe sepsis, VAP or CAUTI between the SVPE-treated patients with GBS and 24 hospital control patients without GBS treated using a CVC in the same ICU or HDU (Fig. 2). However, antimicrobial agents were used more frequently, usually prophylactically, in the hospital control patients compared to the patients with GBS treated with SVPE ($p < 0.0001$; Fig. 2). The

probability of detecting microorganisms in clinical infections may have been reduced due to overzealous use of antibiotics in the hospital control patients. Early trials of PE in patients with GBS showed 34% of patients develop severe infections.[7 11] Subsequently, another large trial documented septicaemia in 19% of patients.[5] However, the rates of CLABSI were not reported. The volume exchanged during SVPE is within the range recommended as per one large RCT on PE [120-200 mL/kg (standard PE)[7] vs. 140 mL/kg for SVPE]. In GBS exchange of 6 L of plasma in adult patients is clinically beneficial in mild to moderate cases and less effective than exchange of 12 L in severe cases, however exchanging 18 L provides no added benefit over 12 L in severe cases of GBS.[5] This suggests that the correlation between clinical benefit and the volume of plasma removed is not linear and exchanging more than 6 L of plasma is likely to have a beneficial effect. During the piloting of the SVPE procedure we assessed that removal of 1 L of patient plasma could be feasible in a day. Therefore we defined our target plasma volume of 8 L to be removed in 8 days. We were able to remove >120 mL/kg plasma in 80% of patients, which should provide a therapeutic effect.[37] Notably, the body weight of our patients may be lower than that of patients in western countries. In addition, SVPE was complete within 8 days, shorter than the usual time required for a full session of PE (10 to 14 days).

Replacement fluid used in SVPE was FFP. We have several justifications in favour of using FFP instead of human albumin or other available colloidal solutions available in Bangladesh. First FFP is safe in terms of microbiological safety since stringent screening for viral and bacterial contamination was performed before infusion. Second, in contrast to human albumin and colloid solutions, FFP contains normal human IgG that could contribute beneficial immunotherapeutic effect in GBS and previously used as replacement fluid in large PE trials.[4 5] SVPE treated GBS patients received approximately half the amount of IgG from the FFP used as replacement fluid compared to the total IVIg doses traditionally used in GBS (2gm/kg). Third, FFP contains all

human plasma proteins that helps preservation of plasma colloid osmotic pressure and prevents formation of oedema and hypotension. Lastly FFP is much cheaper than commercial human albumin.

In each day three units of FFP were transfused as replacement fluid after the last session of SVPE and in the initial two to three sessions, normal saline was used as replacement fluid. This was done to achieve the maximum immunotherapeutic effect of FFP as SVPE was not resumed before the next day and the IgG in FFP remained in the circulation overnight for a longer period of time (10 to 12 hours). However due to long half life of IgG this effect may have reduced due to repeated plasma removal between the transfusion of FFP throughout the course of SVPE.

In GBS, treatment with modified methods of PE done previously, were device based and done on limited number of GBS patients. In one study on 25 GBS patients from India, daily removal of small volume of plasma (10-15 ml plasma/kg body weight) for duration of median 3 days using traditional PE machine was shown to be clinically beneficial.[38] In another study from the same country, 12 GBS patients were treated with PE over 10 days using different PE-machine kit (REF627 kit from Haemonetics Corporation Limited on MCS+ machine) where authors claimed clinical improvement, however the main focus was on cost effectiveness and the total plasma volume exchanged per patient was not mentioned.[39] Nevertheless these methods are based on specific devices those are not in common practice, nor the trained personnel for these are available in the developing countries.

Important observations in terms of secondary endpoints were transient hypotension, transfusion reaction to FFP and minor bleeding through the CVC insertion site. Hypotension is a common complication during traditional PE that affects nearly half of patients.[5] Spells of hypotension

during SVPE were more frequent during the three to four days after initiation of SVPE, and could be easily corrected by rapid infusion of 300-400 mL saline (Fig. 1). The hypotension could possibly be explained by hypovolemia due to drawing blood or as a result of the compromised autonomic nervous system in patients with GBS. As SVPE proceeded, hypotensive spells were encountered less frequently despite drawing the same volume of blood, which may in part be explained by adaptation of the vasomotor system or recovery from autonomic dysfunction. Minor bleeding through the CVC insertion site occurred in 50% of patients and could be controlled by applying a simple pressure pack over the CVC insertion site in most cases; mild prolonged PT was noted in 30% (3/10) patients. However, spontaneous bleeding usually occurs if the PT is more than 2.5 times prolonged and PC is < 0.50 lac/μL.[40] Movement of the limb where the CVC was placed may have caused traction on the CVC and contributed to local bleeding in the other seven patients. Haematuria is not uncommon in patients with a UTI, as may have occurred in one SVPE treated patient; traumatic traction of the urinary catheter may cause haematuria in two other catheterized SVPE-treated patient taking oral aspirin, who had haematuria and sterile urine. We also monitored the major organ function and biochemical status of the patients treated with SVPE. No patients experienced hepatic or renal impairment. One patient developed anaemia and hypoalbuminemia; this patient had severe sepsis, a common cause of anaemia and hypoalbuminemia in critically ill patients admitted to an ICU (patient 11, Fig. 1). Electrolyte imbalances were detected in 15% of the SVPE-treated patients with GBS, and were mild, subclinical and easily corrected.

The median reported durations to recovery of independent walking in patients with GBS in large-scale RCTs after PE are 53, 52 and 70 days[4 5 7]; compared to 30 days in our patients treated with SVPE. Moreover, 60% of the patients with GBS treated with SVPE were able to walk independently at four weeks, whereas 20% of patients with GBS acquired independent walking

ability at four weeks after traditional PE. However, these differences may possibly be due to the small sample size and variations in demographic and neurophysiological characteristics between cohorts. Finally, SVPE was completed in all 20 patients and no patients died.

Limitations of SVPE

SVPE is a time-consuming and labour-intensive procedure, which is a limitation. We used multiple thin-lumen tubing systems interconnected with a multichannel connecter device, which may increase the chance of blood coagulating within the tubing system. Coagulation may require manipulation or replacement of the tubing to ensure free flow of blood and saline. Such handling could increase the chance of microbial contamination. A single continuous wide-lumen tubing system (SVPE kit) could resolve this problem. Most importantly, personnel conducting the SVPE procedure should maintain proper aseptic technique, which can sometimes be challenging in developing countries. Furthermore, other adaptions such as provision of a larger blood bag or increasing the number of days for SVPE could be considered to increase the plasma exchange rate.

Clinical implications and future research

Despite the limitations, our study showed SVPE is a safe and feasible treatment for GBS in a resource-limited setting where IVIg or PE are either unavailable or unaffordable. Specifically, the poorest 20% of the world's population (1.8 billion people) who typically earn less than 10 US$ per day and who are not covered by a national health insurance system may benefit. Considering the incidence of GBS is 2/100,000 in developing countries, approximately 40,000 patients could potentially benefit from SVPE every year, worldwide. In the future, a multicentre RCT is required to assess the clinical efficacy of SVPE for patients with GBS. If proven effective, SVPE could be an affordable and easily available alternative plasma exchange technique in low-income

countries for patients with GBS and other disorders, who at present cannot afford standard PE due to its high cost and unavailability.

Declarations

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Authors' contributions: BI, PVD, BJ, QDM, ZI, and HPE conceived the study design and sample size of the study. MV, MVJ, SR, and HPE contributed to the infection safety guidelines in the study design. BI and QDM conducted the study and BI collected and analysed the data and drafted the manuscript. All authors have critically revised the manuscript and have read and approved the final manuscript.

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Ethics approval and consent to participate: The Institutional Review Board (IRB) of the icddr,b, comprised of an Ethical Review Committee (ERC) and Research Review Committee (RRC), reviewed and approved this study protocol on 09/12/2015 (reference number: PR-15086, version no 3).

Patient consent: Obtained.

Data sharing: The dataset is available from the lead author on request.

Transparency: The corresponding author affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1: Demographic and clinical characteristics of the 20 patients with GBS included in this small volume plasma exchange (SVPE) study at entry

Characteristic		Value
Demography		
Sex [males: females (ratio)]		13:7 (1.85)
Age (years) ¶		33 (18 - 55)
Body weight (kg) ¶		60 (50 -72)
Antecedent events ‡ (total)		18 (90%)
Diarrhoea		10 (50%)
Respiratory infection		5 (25%)
Fever		3 (15%)
Days from antecedent events to weakness ¶		7 (3 - 30)
Days between onset of weakness to admission ¶		7 (2-12)
Neurological deficits at entry		
Weakness in arms and legs		20 (100%)
Cranial nerve deficits		12 (60%)
Decreased deep tendon reflexes		20 (100%)
Sensory involvement		5 (25%)
GBS disability score §	4	19 (95%)
	5	1 (5 %)
Severity of weakness (MRC sum-score) ¶		20 (0-29)
Autonomic dysfunction		11 (55%)

¶ Median (range); † increased protein level (> 45 mg/dL) in combination with CSF cell count < 50/µL; CSF = cerebrospinal fluid; NCS = nerve conduction study; ‡ symptoms of an infection in the four weeks preceding the onset of weakness; § GBS disability score (0 - 6) = 0: healthy state; 1: minor symptoms and capable of running; 2: able to walk 10 meters or more without assistance but unable to run; 3: able to walk 10 meters across an open space with help; 4: bedridden or chair-bound; 5: requiring assisted ventilation for at least part of the day; 6: dead.

Table 2: Treatment characteristics and complications associated with SVPE in the 20 patients with GBS

Characteristic/complication	Value
Treatment characteristics	
Number of sessions of SVPE per patient ¶	30 (24 - 42)
Volume of plasma removed per patient ¶	8.4 (6.3 – 9.6)
Plasma exchange rate (mL/kg) ¶	140 (110-175)
Time between hospital admission and SVPE (days) ¶	8 (5-10)
Time between onset of weakness and start of SVPE (days) ¶	8 (5-10)
Need to stop SVPE due to poor hemodynamic tolerance	0/20 (0%)
Need for blood transfusion for anaemia	1/20 (5%)
Reduction of anticoagulant drug dose for bleeding	3/20 (15%)
Temporary withdrawal of antiplatelet drug for bleeding	4/20 (20%)
Increased anticoagulant drug dose to continue SVPE	1/20 (5%)
CVC blockade/replacement	0/20 (0%)
Complications during SVPE	
Infection	
Leukocytosis	7/20 (35%)
CLABSI §	6.25
VAP §	136.4
CAUTI §	40
Severe sepsis	1/20 (5%)
Antimicrobial agents used	6/20 (30%)
Bleeding and coagulation	
Bleeding from CVC insertion site	10/20 (50%)
Bleeding from mucosal area	3/20 (15%)
Prolonged BT (BT > 10 min)	0/20 (0%)
Prolonged CT (CT > 15 min)	0/20 (0%)
Prolonged PT (PT > 14 sec) ¶	6/20 (30%) [15-19 sec]

Prolonged aPTT (aPTT > 40 sec) ¶	3/20 (15%) [51-240 sec]
Other complications	
Saline responsive hypotension	10/20 (50%)
Anaemia (Hb < 8 gm/L)	2/20 (10%)
Thrombocytopenia (PC < 1.5 lac/µL) ¶	6/20 (30%) [0.79-1.3 lac/µL]
Jaundice (serum bilirubin > 1.2 mg/dL)	0/20 (0%)
Renal impairment (serum creatinin > 1.2 mg/dL)	0/20 (0%)
Hyponatraemia (serum Na^+ < 135 mEq/L)	1/20 (5%) [126 mEq/L]
Hypokalaemia (serum K^+ < 3.5 mEq/L) ¶	3/20 (15%) [2.6-3.2 mEq/L]
Hypoalbuminemia (serum albumin > 35 gm/L) ¶	4/20 (20%) [26-32 gm/L]
Hypocalcaemia (serum Ca^+ < 2.2 mmol/L) ¶	3/20 (15%) [1.89-1.98 mmol/L]
Hypomagnesaemia (serum Mg^+ < 75 mEq/L) ¶	1/20 (5%) [73 mEq/L]
Hypersensitivity/transfusion reaction to FFP	4/20 (20%)

¶ Median (range); § rate per 1000 device days; CLABSI: central line-associated bloodstream infection; VAP: ventilator-associated pneumonia; CAUTI: catheter-associated urinary tract infection; CVC: central venous catheter; BT: bleeding time, CT: clotting time; PT: prothrombin time; APTT: activated partial thromboplastin time; FFP: fresh frozen plasma.

Table 3: Neurological outcomes of the 20 patients with GBS after SVPE

Clinical outcome	1 month	2 months	3 months	6 months
Cranial nerve involvement	7/20 (35%)	6/20 (30%)	4/20 (20%)	2/20 (10%)
Autonomic involvement	3/20 (15%)	3/20 (15%)	0/20 (0%)	0/20 (0%)
Sensory dysfunction	1/20 (5%)	1/20 (5%)	1/20 (5%)	1/20 (5%)
GBS disability score¶	0 = 0	0 = 1	0 = 1	0 = 2
	1 = 3	1 = 6	1 = 7	1 = 7
	2 = 9	2 = 6	2 = 6	2 = 5
	3 = 2	3 = 1	3 = 1	3 = 3
	4 = 3	4 = 5	4 = 5	4 = 3
	5 = 3	5 = 1	5 = 0	5 = 0
MRC sum score † ⁎	47 (0-60)	49 (0-60)	53 (6-60)	58 (22-60)
ONLS ‡ ⁎	4 (1-12)	3 (0-12)	3 (0-12)	2 (0-10)
R-ODS § ⁎	26 (0-41)	33 (0-45)	37 (0-45)	38 (0-46)

⁎ Median (range); ¶ GBS disability score (0 - 6) = 0: healthy state, 1: minor symptoms and capable of running, 2: able to walk 10 meters or more without assistance but unable to run, 3: able to walk 10 meters across an open space with help, 4: bedridden or chair-bound, 5: requiring assisted ventilation for at least part of the day, 6: dead; † MRC sum score: Medical Research Council sum score; ‡ ONLS: Overall Neuropathy Limitation Scale [22]; § R-ODS: Rash-built Overall Disability Score [23]

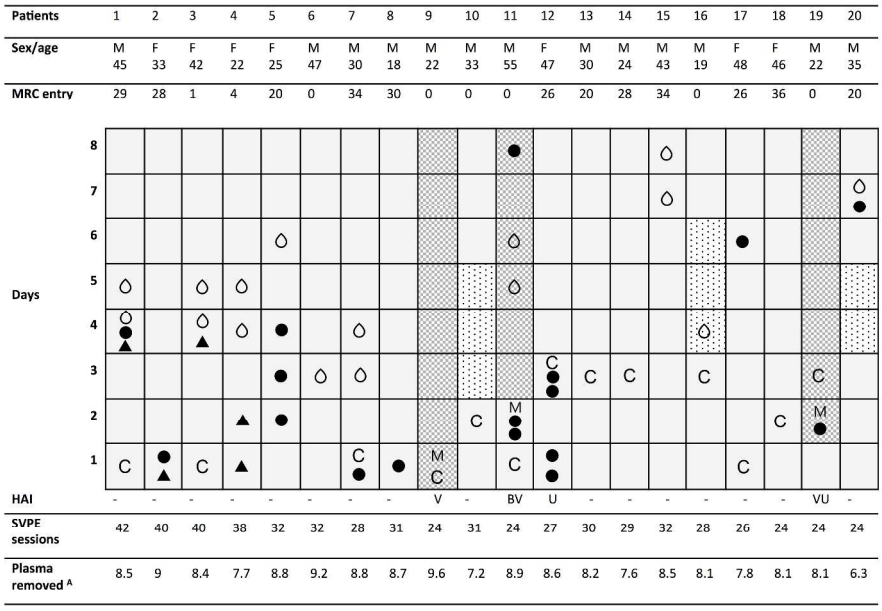
Figure 1: Feasibility of SVPE and associated complications for the 20 individual patients with GBS.

SVPE: small volume plasma exchange, HAI: hospital acquired infection, V: ventilator-associated pneumonia, B: central line-associated blood stream infection, U: catheter-associated urinary tract infection, [A] measured in litres, ●: spell of hypotension (systolic BP < 90 mm Hg), ◊: CVC insertion site bleeding, ▲: hypersensitivity to fresh frozen plasma, shaded squares: pyrexia due to bacterial infection, dotted squares: pyrexia due to suspected viral infection, M: onset of mechanical ventilation, C: urinary catheterization.

Figure 2: Hospital-acquired infections and use of antibiotics in the 20 patients with GBS receiving SVPE compared to the 24 hospital control patients without GBS treated in an ICU with a CVC who did not receive SVPE.

■ SVPE (n = 20): twenty patients with GBS aged ≥ 18-years-old who were bedbound (GBS disability score ≥ 4) received small volume plasma exchange (SVPE) within 2 weeks of the onset of weakness. ⊡ Non-SVPE (n=20): twenty-four patients aged ≥ 18-years-old with a diagnosis other than GBS who required a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units in the same period as the patients with GBS received SVPE; ∗ $p < 0.0001$.

Figure 3: Kaplan-Meier estimate (with 95% confidence limits) of the cumulative incidence of restoration of independent walking ability in patients with GBS treated with SVPE.



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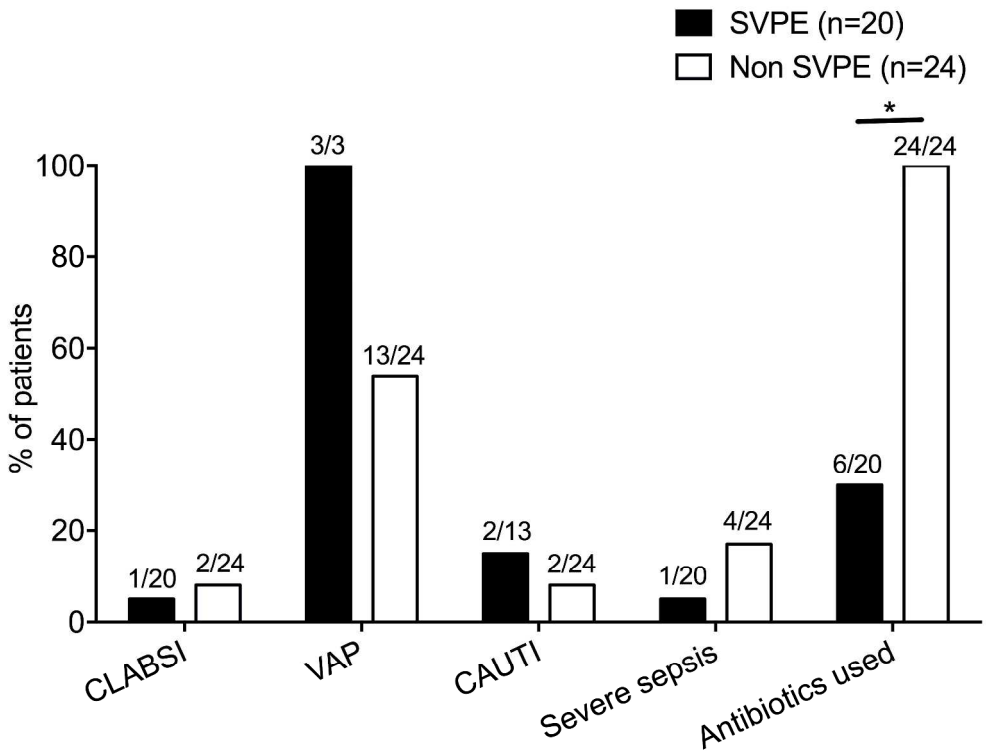

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■ SVPE (n = 20): twenty patients with GBS aged ≥ 18-years-old who were bedbound (GBS disability score ≥ 4) received small volume plasma exchange (SVPE) within 2 weeks of the onset of weakness. ⊡ Non-SVPE (n=20): twenty-four patients aged ≥ 18-years-old with a diagnosis other than GBS who required a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units in the same period as the patients with GBS received SVPE; * $p < 0.0001$.

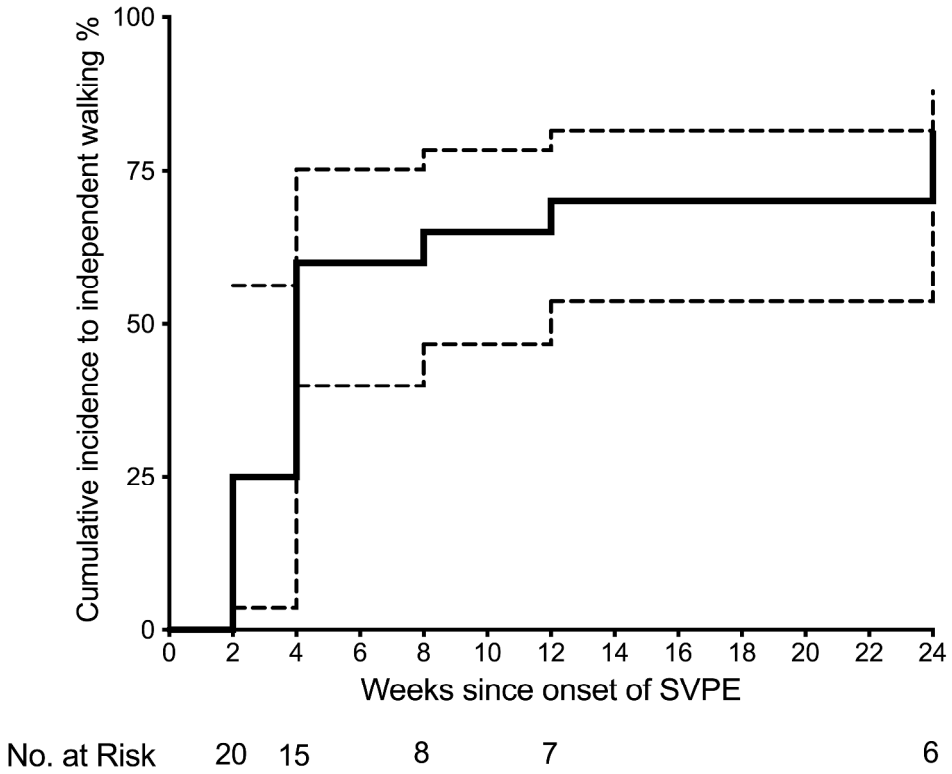
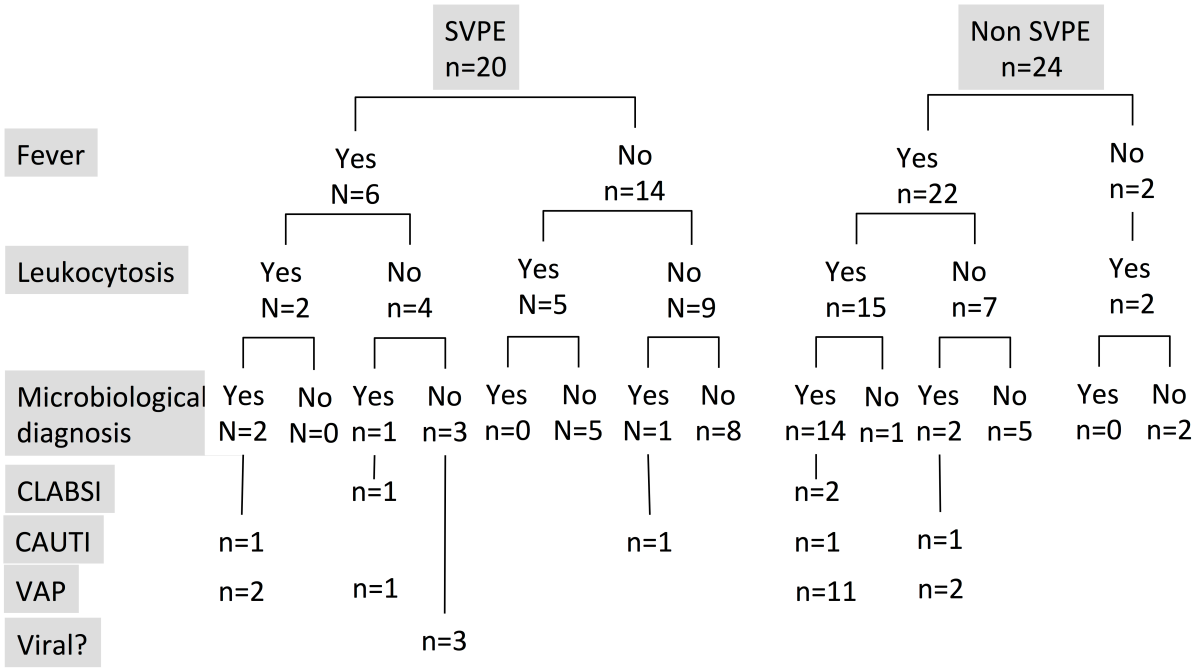


Figure 3: Kaplan-Meier estimate (with 95% confidence limits) of the cumulative incidence of restoration of independent walking ability in patients with GBS treated with SVPE.

Supplementary Figure: Hospital-acquired infections in the 20 patients with GBS treated with SVPE and the 24-hospital control patients without GBS.



SVPE: small volume plasma exchange, CLABSI: central line-associated blood stream infection, CAUTI: catheter-associated urinary tract infection, VAP: ventilator-associated pneumonia.

2017 CONSORT checklist of information to include when reporting a randomized trial assessing nonpharmacologic treatments (NPTs)*. Modifications of the extension appear in italics and blue.

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
Title and abstract					
	1a	Identification as a randomized trial in the title	NA (Non-randomized)		
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3, 4, 5	Refer to CONSORT extension for abstracts for NPT trials	3, 4, 5
Introduction					
Background and objectives	2a	Scientific background and explanation of rationale	6		
	2b	Specific objectives or hypotheses	6, 7		
Methods					
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7	When applicable, how care providers were allocated to each trial group	NA
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	No changes to methods after trial commencement		
Participants	4a	Eligibility criteria for participants	7, 8	When applicable, eligibility criteria for centers and for care providers	NA
	4b	Settings and locations where the data were collected	7		
Interventions†	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7, 8	Precise details of both the experimental treatment and comparator	7, 8
	5a			Description of the different components of the interventions and, when applicable, description of the procedure for tailoring the interventions to individual participants.	9
	5b			Details of whether and how the interventions were standardized.	8, 9

Cite as: *Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40–7.*

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
	5c.			Details of whether and how adherence of care providers to the protocol was assessed or enhanced	8, 9
	5d			Details of whether and how adherence of participants to interventions was assessed or enhanced	NA
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9		
	6b	Any changes to trial outcomes after the trial commenced, with reasons	No changes to trial outcomes after the trial commenced		
Sample size	7a	How sample size was determined	9	When applicable, details of whether and how the clustering by care providers or centers was addressed	NA
	7b	When applicable, explanation of any interim analyses and stopping guidelines	10		
Randomization:					
- Sequence generation	8a	Method used to generate the random allocation sequence	NA (Non-randomized)		
	8b	Type of randomization; details of any restriction (such as blocking and block size)	NA (Non-randomized)		
- Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	NA (Non-randomized)		
- Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	NA (Non-randomized)		
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Blinding was not possible	If done, who was blinded after assignment to interventions (e.g., participants, care providers, those administering co-interventions, those assessing outcomes) and how	Blinding was not possible

Cite as: *Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40–7.*

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
	11b	If relevant, description of the similarity of interventions	7, 8		
	11c			If blinding was not possible, description of any attempts to limit bias	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10	When applicable, details of whether and how the clustering by care providers or centers was addressed	NA
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NA		
Results					
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	11	The number of care providers or centers performing the intervention in each group and the number of patients treated by each care provider or in each center	Single center study
	13b	For each group, losses and exclusions after randomization, together with reasons	No losses and exclusions after inclusion		
	13c			For each group, the delay between randomization and the initiation of the intervention	11
	new			Details of the experimental treatment and comparator as they were implemented	11-16
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7		
	14b	Why the trial ended or was stopped	NA (Trial completed)		
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1	When applicable, a description of care providers (case volume, qualification, expertise, etc.) and centers (volume) in each group.	NA
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11-12		

Cite as: *Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40–7.*

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12-16		
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA		
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	15		
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12-15		
Discussion					
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	20	In addition, take into account the choice of the comparator, lack of or partial blinding, and unequal expertise of care providers or centers in each group	NA
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	16-20	Generalizability (external validity) of the trial findings according to the intervention, comparators, patients, and care providers and centers involved in the trial	16-20
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16-20		
Other information					
Registration	23	Registration number and name of trial registry	4		
Protocol	24	Where the full trial protocol can be accessed, if available	Manuscript reference no: 17		
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	21		

**Additions or modifications to the 2010 CONSORT checklist. CONSORT = Consolidated Standards of Reporting Trials*
†The items 5, 5a, 5b, 5c, 5d are consistent with the Template for Intervention Description and Replication (TIDieR) checklist

Cite as: *Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40–7.*

Table: Required documents of the safety and feasibility study of the small volume plasma exchange (SVPE) for Guillain-Barré syndrome patients for the World Health Organization Trial Registration Data Set

	Item/Label	Description
1	Primary Registry and Trial **Identifying** Number	Clinicaltrials.gov NCT02780570
2	Date of Registration in Primary Registry	May 23, 2016
3	Secondary Identifying Numbers	International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) Protocol Number: PR-15086, Version no. 3, Date: 09/12/2015
4	Source(s) of Monetary or Material Support	GBS/CIDP Foundation International Fondation Mérieux: (Small Grants Program 2015)
5	Primary Sponsor	GBS/CIDP Foundation International
6	Secondary Sponsor(s)	Fondation Mérieux: (Small Grants Program 2014)
7	Contact for public queries	MD. BADRUL ISLAM Email: bislamdmch@gmail.com Telephone no: +880 1712 89 0172 Postal address: Dr. Badrul Islam

		Research trainee and PhD Fellow Laboratory Sciences and Services Division (LSSD) Icddr,b Dhaka, Bangladesh
8	Contact for scientific queries	MD. BADRUL ISLAM Principal Investigator (PI) Email: bislamdmch@gmail.com Telephone no: +880 1712 89 0172 Postal address: Dr. Badrul Islam Research trainee and PhD Fellow Laboratory Sciences and Services Division (LSSD) Icddr,b Dhaka, Bangladesh
9	Public title	Small volume plasma exchange for Guillain-Barré syndrome
10	Scientific title	Small volume plasma exchange for Guillain-Barré syndrome in low-income countries: a safety and feasibility study
11	Countries of Recruitment	Bangladesh
12	Health condition(s) or problem(s) studied	Guillain-Barré syndrome (GBS)
13	Interventions	*Small Volume Plasma Exchange (SVPE)* A loading dose of low-molecular weight heparin (1.5 mg/kg) will be given subcutaneously at least two hours

before initiation of SVPE; the same dose will be administered once daily or divided into two equal doses daily for eight days or until SVPE is completed. Whole blood (7 mL/kg body weight) will be drawn from the central venous catheter into the blood transfusion bag in each session. The blood bag will be hung beside the patient for 2.5 h on a saline stand and left uninterrupted to allow plasma and blood cells to separate. The blood cells will be infused back into the patient and plasma will be discarded and replaced with fresh frozen plasma and colloid solution alternately (in equal volumes) via the closed-circuit SVPE kit illustrated in. In case of excessive clotting (bleeding time reduction of > 50% of baseline for that patient), aspirin (600 mg) will be administered orally at least two hours before the next SVPE session and continued thereafter at 150 mg orally/day until SVPE is completed. One blood bag will be used each day, with a total of six sessions/day. A total of 48 sessions will be performed over eight days, removing approximately 8000 mL plasma in total.

Central venous catheterized patients without GBS

To compare the safety of SVPE in patients with GBS in the context of the background risk of central line-associated blood stream infection (CLABSI) at the study intensive care (ICU) and high-dependency care (HDU) units, the incidence of CLABSI will be assessed in a control group of adult patients with a diagnosis other than GBS admitted to the same ICU and HDU units in the same period of time the patients with GBS will be enrolled for SVPE. We will assess the rate of CLABSI in

		patients aged ≥ 18-years-old requiring a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units.
14	Key Inclusion and Exclusion Criteria	*Inclusion criteria for SVPE in GBS patients* 1. Patients aged ≥ 18-years-old fulfilling the diagnostic criteria for GBS of the National Institute of Neurological and Communicative Disorders and Stroke (NINDS) 2. Unable to walk unaided for more than 10 meters (GBS disability score ≥ 3) 3. Presented within 2 weeks of the onset of weakness 4. Unable to afford standard treatment with IVIg or PE. *Exclusion criteria for SVPE in GBS patients* 1. Patients with severe or terminal concomitant illness 2. Evidence of healthcare-associated infection on admission (except for aspiration pneumonia) 3. Previous history of severe allergic reaction to properly matched blood products and pregnant women will be excluded from the study. *Inclusion criteria for patients without GBS* 1. Patients aged ≥ 18-years-old 2. Requiring a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units in the same period of time the patients with GBS enrolled for SVPE. *Exclusion criteria for patients without GBS*

		1. Patients with healthcare-associated infection present on admission (except aspiration pneumonia) 2. Pregnant women
15	Study type	*Type of the study*: Interventional *Method of allocation:* Non-randomized *Masking:* Non-masked *Assignment:* Parallel arm • SVPE in patients with GBS • Rate of CLABSI in patients without GBS *Purpose:* Safety and feasibility of SVPE
16	Date of first enrolment	February 20, 2016
17	Target sample size	SVPE in patients with GBS = 20 Rate of CLABSI in patients without GBS = ≥ 20
18	Recruitment status	Completed: • Twenty cases of GBS have been successfully treated with SVPE and 24 control cases without GBS have been recruited.
19	Primary Outcome(s)	*Primary outcome of safety*: 1. Number of patients with GBS treated with SVPE developing severe sepsis or septic shock due to central line associated blood stream infection (CLABSI) as per standard guideline (Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central line-associated Bloodstream Infection); CDC Device-associated Module, BSI. January 2017) 2. Occurrence of venous thrombosis in the limb

		where the CVC is placed. Venous thrombosis will be assessed according to Wells criteria (*Philip S. Wells et al. Evaluation of d -Dimer in the Diagnosis of Suspected Deep-Vein Thrombosis; N Engl J Med 2003;349:1227-35*) <u>*Primary outcome of feasibility*</u>: 1. Ability to remove at least eight litres of plasma by SVPE over eight days.
20	Secondary Outcome(s)	<u>*Secondary outcome of safety*</u>: 2. Relative risk of CLABSI due to SVPE compared to CLABSI in control patients without GBS treated using a CVC 3. Hemodynamic instability during the SVPE procedure (variations in systolic blood pressure greater than 30 mmHg or sudden bradycardia involving a reduction in heart rate by more than 20 beats per min within 30 min of starting SVPE or an increase in heart rate above 120 beats per min) 4. Development of anaemia (Hb <7 gm/dL) or serious haemorrhage requiring blood transfusion. <u>*Secondary outcome of feasibility*</u>: 1. Rate of CVC occlusion during the SVPE procedure 2. The healthcare personnel's acceptability and

		satisfaction with the SVPE procedure and any unanticipated events compromising the SVPE procedure as assessed using a standard questionnaire. 3. Neurological outcome will be assessed in terms of improvement in GBS disability score and MRC sum score at discharge and up to 4 weeks after entry.

BMJ Open

Small volume plasma exchange for Guillain-Barré syndrome in resource-limited settings: a phase II safety and feasibility study

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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Medical management
Keywords:	Guillain-Barré syndrome, Small volume plasma exchange, Safety, Feasibility

Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.

SUPPLEMENTARY VIDEO.mp4

Title:

Small volume plasma exchange for Guillain-Barré syndrome in resource-limited settings: a phase II safety and feasibility study

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ABSTRACT

OBJECTIVE

To assess the safety and feasibility of small volume plasma exchange (SVPE) as an alternative to standard plasma exchange (PE) or intravenous immunoglobulin (IVIg) for Guillain-Barré syndrome (GBS) patients.

DESIGN

Non-randomized, single arm, interventional trial.

SETTING

National Institute of Neurosciences and Hospital, Dhaka, Bangladesh.

PARTICIPANTS

Twenty adult (>18 years) patients with GBS presented within 2 weeks of onset of weakness who were unable to walk unaided for more than 10 meters.

INTERVENTIONS

SVPE involves blood cell sedimentation in a blood bag and removal of supernatant plasma after blood cells are re-transfused. This procedure was repeated three to six times a day, for eight consecutive days.

OUTCOME MEASURES

Serious adverse events (SAE) were defined as severe sepsis and deep venous thrombosis related to the central vein catheter (CVC) used during SVPE. SVPE was considered safe if less than 5/20 patients experienced a SAE, and feasible if 8 L plasma could be removed within 8 days in at least 15/20 patients.

RESULTS

Median patient age 33 years (IQR 23-46; range 18-55); 13 (65%) were male. Median MRC sum score was 20 (IQR 0-29; range 0-36); three (15%) patients required mechanical ventilation. One patient developed SAE (severe sepsis, possibly related to CVC). Minor adverse effects were

transient hypotension in 10 (50%) patients; CVC-associated bleeding in 10 (50%); transfusion reaction to fresh frozen plasma in 4 (20%); and hypo-albuminemia, anaemia or electrolyte imbalance in 4 (20%). Removal of 8 L plasma was possible in 15 (75%) patients. GBS disability score improved by at least one grade in 14 (70%) patients four weeks after SVPE started. No patients died.

CONCLUSION

SVPE seems a safe and feasible alternative treatment to standard PE or IVIg for GBS; further studies of clinical efficacy in low-resource developing countries are warranted.

TRIAL REGISTRATION

Clinicaltrials.gov NCT02780570 on May 23, 2016

Strength and limitations of the study:

1. The strength of this study underlies the novel and simple technique of SVPE, which is much less expensive than conventional immunotherapies (plasma exchange and intravenous immunoglobulin)
2. SVPE is corroborated as safe and feasible for the first time in a prospective and standardized cohort of patients with Guillain-Barré syndrome (GBS).
3. The intrinsic limitations of this study are its non-randomized, single arm nature, which is conducted in a single center with a limited sample size of GBS patients.
4. Clinical efficacy of SVPE on patients with GBS was a secondary end-point assessment and therefore deserves a randomized controlled trial in future to assess the clinical efficacy of SVPE for the patients with GBS.

Introduction

Guillain-Barré syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy with a yearly incidence of 1.2 to 2.3 cases per 100,000 per year.[1] GBS is characterized by rapidly progressive limb weakness and, in a proportion of cases, respiratory failure (25%) or severe autonomic dysfunction (10%). Plasma exchange (PE) was the first treatment proven to be effective for GBS, if given within 4 weeks of the onset of weakness.[2-11] Conventionally for GBS patients, three to five plasma exchange sessions are done in alternate days within a span of 7 to 14 days targeting a plasma exchange rate of 120 - 200 ml/kg (40-50ml/kg/day).[7]. Later studies showed treatment with intravenous immunoglobulin (IVIg) (0.4 g/kg per day for 5 days) has a similar efficacy as PE in patients with GBS who are unable to walk, if started within 2 weeks of the onset of weakness.[12 13]

Unfortunately, most patients in low-income countries cannot afford expensive treatment with either PE or IVIg.[14] In Bangladesh, a full course of IVIg for a 60 kg adult costs approximately 12,000-16,000 US$ and treatment with conventional PE for 5 days costs approximately 4,500-5,000 US$. The mean income in Bangladesh was 4 US$ per day in 2016 (World Bank and Bangladesh Bureau of Statistics 2016); IVIg and PE cost the equivalent of 3,000 and 1,250 mean income days, respectively. At present, the majority (92%) of patients with GBS in Bangladesh receive supportive care only.[14] In addition, mobile PE equipment is not available in Bangladesh; therefore, patients admitted to the intensive care unit (ICU) cannot receive PE. We previously reported the mortality rates for GBS in Bangladesh range from 12 to 14% and observed 29% of patients with GBS in Bangladesh are unable to walk at 6 months after onset; these poor outcomes are undoubtedly due to the low rates of specific treatment with PE or IVIg.[15 16]

Small volume plasma exchange (SVPE) may represent a cheap, effective alternative treatment for GBS. SVPE is based on the same principle as conventional PE (selective removal of plasma) but uses a novel, simple technique with much lower costs (approximately 500 US$). The current non-randomized trial was designed to investigate the safety and feasibility of SVPE in 20 patients with GBS admitted to the National Institute of Neurosciences Hospital in Dhaka, Bangladesh.

Methods/Design

Study design

For this non-randomized, single arm, interventional safety and feasibility trial, 20 adult patients with GBS were enrolled between March 2016 and December 2016 for SVPE at the National Institute of Neurosciences and Hospital (NINS), Dhaka, Bangladesh. A detailed study protocol was published previously and includes definitions of all variables used in this study.[17]

Four to six daily sessions of whole blood sedimentation and removal of supernatant plasma after re-transfusion of the sedimented blood cells was planned for the 20 patients with GBS, with a target of removing an overall volume of at least 8 litres (L) of plasma over a total of 8 days.[17] (See supplementary video for SVPE procedure)

Patients with GBS were monitored according to a standard protocol throughout the course of SVPE until the second day after withdrawal of the central venous catheter (CVC) in order to assess predefined measures of safety and feasibility and followed up for six months to assess neurological outcome. The protocol was reviewed and approved by the institutional research and ethics review committees at the icddr,b and registered at clinicaltrials.gov (NCT02780570).[17] All patients provided written informed consent to participate in this study.

Patient and Public Involvement

Patients and or public were not involved either in the development of the research question, study design and outcome measure or recruitment to and conduct of the study.

Inclusion and exclusion criteria for patients with GBS

Patients aged ≥ 18-years-old fulfilling the diagnostic criteria for GBS of the National Institute of Neurological and Communicative Disorders and Stroke (NINDS)[18] were enrolled, provided they were unable to walk unaided for more than 10 meters (GBS disability score ≥ 3), presented within 2 weeks of the onset of weakness, and were unable to afford standard treatment with IVIg or PE. Patients with concomitant severe or terminal illnesses, evidence of healthcare-associated infection (HAI) on admission (except for aspiration pneumonia), a previous history of severe allergic reactions to properly matched blood products, and pregnant women were excluded from the study.

Control cohort

To compare the safety of SVPE in patients with GBS in the context of the background risk of central line-associated blood stream infection (CLABSI) at our institution, we prospectively assessed the incidence of CLABSI in a hospital control group of 24 adult patients without GBS receiving neurocritical care. Hospital controls were eligible based on the following characteristics: ≥ 18-years-old, a neurological diagnosis other than GBS, and a CVC placed for > 2 and ≤ 8 calendar days after admission to the same ICU or HDU unit as the SVPE-treated patients. Patients with a HAI (except aspiration pneumonia) and pregnant women were excluded from the control group.

Primary and secondary outcome measures

The primary outcome measures of safety were the number of patients with GBS treated with SVPE who developed either severe sepsis or septic shock due to CLABSI[19] and the occurrence of venous thrombosis in the limb where the CVC was placed. The primary outcome measure of feasibility was the ability to remove at least 8 L of plasma over 8 days.

The secondary outcome measures of the safety of SVPE were the relative risk of CLABSI due to SVPE (compared to CLABSI in the hospital control group without GBS), hemodynamic instability during the SVPE procedure, and development of anaemia (Hb < 8 gm/dL) or any catheter-related haemorrhage requiring a blood transfusion.

The secondary outcome measure of feasibility of SVPE was the rate of CVC occlusion during the SVPE procedure. In addition, neurological outcome was assessed using the GBS disability score[20], MRC sum score[21], Overall Neuropathy Limitation Scale (ONLS)[22] and Rasch-built Overall Disability Scale (R-ODS)[23] at 1st, 2nd , 3rd , and 6th months from the start of SVPE.

Procedure safety documentation and cost of SVPE

Strict aseptic procedures were followed to prevent CLABSI.[24-26] SVPE was documented in terms of the duration and amount of plasma removed in each session, and the type and volume of replacement fluid and fresh frozen plasma (FFP) used. Throughout the procedure, the haemodynamic, haematological, biochemical, coagulation and infection profiles of the SVPE-treated patients were monitored according to the protocol.[17] Screening for hepatitis B and C viruses, human immunodeficiency virus (HIV) and syphilis were performed as patient baseline assessments, and also on donor FFP before administration. CLABSI, primary and secondary bloodstream infections[19], catheter-associated urinary tract infection (CAUTI)[27], ventilator-associated pneumonia (VAP)[28] and other HAI[29 30] were documented in the SVPE-treated patients with GBS and the hospital control group. Expenditure for the full course of SVPE will be

approximately 500 US$ [fresh frozen plasma (24 bags) = 240 US$, blood bag and saline sets: 40 US$, low molecular weight heparin: 110 US$, routine investigation: 50 US$, saline: 10 US$, CV catheter: 40 US$ = total 490 US$].

Sample size

This safety and feasibility study enrolled 20 patients with GBS for SVPE. We could not perform a formal power calculation for this safety and feasibility study. The sample size was based on previous pilot studies conducted in GBS.[31 32] The baseline rate of CLABSI was measured in the hospital control group of 24 patients without GBS admitted to the same study facility who required a CVC for at least 8 days during the study period.

Stopping rules for the trial based on safety and feasibility

Decision to stop the SVPE trial was designated using a Bayesian approach.[33-35] Accordingly, a predictive success rate of 75% was predefined for the SVPE procedure. If more than 5 of 20 patients experienced an SAE, or if it appeared impossible to remove at least 8 L of plasma over 8 days in at least 15 of 20 patients, the procedure was considered unsafe or unfeasible.

Statistical analysis

The rate of HAIs (CLABSI, VAP and CAUTI) per 1000 device days were calculated by dividing the number of each HAI during the study period by the number of device days and multiplying the result by 1000. The infection safety profile for SVPE was assessed by calculating the standardized infection ratio to define the risk of HAIs in patients with GBS treated with SVPE. The standardised infection ratio (SIR) was calculated by dividing the number of observed HAI by the number of HAI predicted (i.e., the infection rate in the control

group). The predicted HAI rate was calculated using the rates of HAI in the hospital control group of patients without GBS during the study period. Percentage values were compared using the Chi-square test or Fisher's exact test (two-tailed) and median values, the Mann-Whitney U-test using SPSS 22 software (IBM SPSS Statistics for Windows Version 22.0., IBM Corp., Armonk, NY, USA). Analyses were performed on an intention-to treat basis. All *P*-values reported are two-sided; $p < 0.05$ was considered significant.

Results

Patients and hospital controls

The demographic and clinical characteristics of the 20 patients with GBS are given in Table 1. The median age of the patients with GBS was 33 years (range; 18-55); median body weight was 60 kg (IQR, 55-65 kg; range, 50-72 kg) and 13 (65%) patients were male (Fig. 1). On admission and before the start of SVPE, all 20 patients with GBS were unable to walk independently (GBS disability score, 4). One patient required mechanical ventilation from the second day after the onset of weakness; SVPE was started on the fourth day of mechanical ventilation (patient 9, Fig. 1). Two of the 19 patients who did not require mechanical ventilation at the start of the study required mechanical ventilation on the second day after initiation of SVPE (patients 11 and 19, 11 and 2 days after the onset of weakness, respectively; Fig. 1). The median MRC sum score for the limb muscles in all 20 patients was 20 (IQR: 0-29; range: 0-36; Fig. 1). Symptoms of a preceding infection in the 4 weeks before the onset of weakness were present in 18 (90%) patients with GBS, of whom 10 (50%) had diarrhoea. Median duration from admission to start of SVPE was two days (IQR, 2-3 days; range, 0-7 days). Median duration to nadir from the onset of weakness was five days (range, 1-13 days). Electrodiagnostic nerve conduction studies indicated 15 (75%) patients had an axonal subtype and 5 (25%) patients had a demyelinating subtype of GBS. Median duration from onset of weakness to NCS examination was 10 days (range, 4-16

days). All patients had albuminocytologic dissociation; median CSF protein was 166 mg/dL (range 117-253 mg/dL). Median duration from onset of weakness to CSF examination was 11 days (range, 4-17 days).

Median age of the 24 hospital control patients without GBS was 44 years (IQR, 25-57; range; 18-74); 10 (42%) were male. Age and gender distribution were not significantly different compared to the 20 patients with GBS ($p = 0.2155$, $p = 0.1434$, respectively). The diagnoses for these 24 patients were: brain tumour ($n = 5$), transverse myelitis ($n = 5$), head trauma after road traffic accident ($n = 3$), viral meningoencephalitis ($n = 2$), myasthenia gravis ($n = 2$), compressive cervical myelopathy ($n = 2$), cerebrovascular accident ($n = 2$), motor neuron disease ($n = 1$), electrolyte imbalance ($n = 1$) and status epilepticus ($n = 1$).

Primary endpoints

One patient with GBS treated with SVPE developed severe sepsis, possibly due to SVPE-related CLABSI (SVPE window-period blood culture revealed methicillin-resistant *Staphylococcus aureus*). This patient required intravenous fluid, noradrenalin infusion and intravenous antibiotics, but eventually improved (patient 11, Fig. 1). This patient also had signs and symptoms suggestive of aspiration pneumonia and VAP; *Streptococcus spp.* was isolated from pulmonary aspirates. Further laboratory results revealed dys-electrolytemia, anaemia and hypo-albuminemia. No patients experienced deep vein thrombosis due to the CVC for SVPE. Fifteen (75%) of the 20 patients met the primary endpoint of feasibility, defined as the ability to remove at least 8 L of plasma in eight days. The median volume of plasma removed was 8.5 L (IQR, 7.9-8.8 L; range, 6.3-9.6 L; Fig. 1). The median plasma exchange rate was 140 mL/kg bodyweight (IQR, 125-155 mL/kg; range, 110-175 mL/kg) over 8 days and 16 (80%) patients had a plasma exchange rate > 120 mL/kg (Table 2).

Secondary endpoints

Infections among SVPE-treated patients with GBS and hospital controls

Among the 20 patients with GBS treated with SVPE, six (30%) had fever during SVPE (Fig. 1, Supplementary Figure 1), including 2 (10%) patients with leucocytosis who were diagnosed with HAI (VAP and CAUTI in one patient; VAP in one patient). In three out of four (20%) patients with fever without leucocytosis, fever subsided within two to three days without antimicrobial therapy (Fig. 1). The remaining patient with pyrexia without leucocytosis had microbiological evidence of both CLABSI and VAP (patient 11, Fig. 1). In all other 14 patients with GBS, no fever was documented during the course of SVPE until the tenth day of SVPE (second day after removal of the CVC for SVPE). Five of these 14 patients had leucocytosis, but no site-specific HAI could be detected. However, one of the nine patients without fever but leucocytosis fulfilled the criteria for CAUTI (patient 12, Fig. 1). All three patients who required mechanical ventilation subsequently developed VAP; two of the 13 patients who required a urinary catheter developed a CAUTI (patient 11, Fig. 1). No patients died during the 6 months follow-up.

All 24-hospital control patients without GBS required mechanical ventilation and an indwelling urinary catheter. Of these patients, 22 (92%) patients had fever, of whom 15 (63%) had leucocytosis; a diagnosis of a specific HAI could be made 14 of these 15 patients (CLABSI in two, CAUTI in one, VAP in 11) and four (17%) fulfilled the criteria for severe sepsis (Supplementary Figure 1). Seven (29%) of the 24 hospital control patients had fever without leucocytosis. In two of these seven patients, a specific HAI was diagnosed (CAUTI and VAP in one, and VAP in one). In two hospital control patients, no fever was documented until day 10 after first placement of the CVC, but leucocytosis was present and no site-specific HAI could be detected (Supplementary Figure 1).

The rates of CLABSI, CAUTI and VAP per 1000 device days in the SVPE-treated patients with GBS were 6.25, 19.2 and 40 compared to 10.4, 10.4 and 67.7 for the hospital control patients without GBS, respectively. The relative risks of CLABSI, CAUTI and VAP associated with SVPE were 0.6, 1.2 and 1.8, respectively, compared to hospital control patients. The rates of CLABSI, CAUTI and VAP were comparable between SVPE-treated patients with GBS and hospital control patients ($p > 0.05$). Antimicrobial agents were used more frequently in the hospital control patients ($p < 0.0001$; Fig. 2). The standardised infection ratios for CLABSI, CAUTI and VAP for SVPE-treated patients with GBS were 0.6, 1.8 and 1.9, respectively.

Other secondary endpoints

Ten (50%) of the 20 patients treated with SVPE experienced transient hypotension during SVPE, which was corrected by infusion of 200-300 mL crystalloid saline (Fig. 1). Minor bleeding through the CVC insertion site (excluding at the time of insertion) was observed in 10/20 patients (50%; Fig. 1); these bleeds required a pressure pack. Reduction of the anticoagulant dose along with a pressure pack was required in 3/20 patients, who all had a prolonged prothrombin time (PT). Three patients had single episode of haemorrhage through the urinary catheter: one was diagnosed with a CAUTI with normal coagulation profile, one had a prolonged PT, the other had sterile haematuria with normal PT. Overall, PT and activated partial thromboplastin time (aPTT) were prolonged in 4/20 patients and only PT was prolonged in 2/20 patients. Clotting time and bleeding time were not prolonged in any patient. One patient developed anaemia (haemoglobin, 8 gm/L) at the end of SVPE; this patient also had severe sepsis and required one unit of blood transfusion (patient 11, Fig. 1). CVC blockages were not observed in any SVPE-treated patients with GBS. One patient with increased clotting tendency who required an increased dose of low molecular weight heparin had shortened clotting time (CT) (< 50% of upper limit of normal), though PT was normal (patient 10, Fig. 1).

The neurological outcomes of the SVPE-treated patients with GBS at six months in terms of neurological scores are given in Table 3. Median time to recover the ability to walk unaided was 4 weeks (Fig. 3). Fourteen (70%) of the 20 patients had an improvement in GBS disability score of one or more grades at four weeks after the onset of SVPE. At one month, 12 patients (60%) were able to walk unaided, two patients (10%) were able to walk aided and six (30%) patients were bedbound, of whom three still required mechanical ventilation. At three months, 14 (70%) patients were able to walk unaided, one (5%) could walk with aid and five (25%) patients were bedbound. At six months, 14 (70%) patients were able to walk unaided, three (5%) could walk with aid and three (15%) remained bedbound (Table 3).

Other relevant clinical and laboratory findings

Allergic/transfusion reaction to FFP was observed in four patients with GBS treated with SVPE (Fig. 1). These transfusion reactions presented as an itchy erythematous skin rash (three patients), fever (two patients), hypotension (one patient) following transfusion of FFP; all of these reactions were managed with oral antihistamine (and intravenous saline in one patient) without further complications.

The other documented haematological and biochemical abnormalities were hypo-albuminemia (n = 4), thrombocytopenia (n = 6), hyponatraemia (n = 1), hypokalaemia (n = 3), hypomagnesaemia (n = 1), hypocalcaemia (n = 3); (Table 2).

Immunoglobulin dosage admitted by FFP

During SVPE the median volume of FFP received per GBS patient as replacement fluid was 6000 ml (range, 5000 ml to 6000 ml). Considering the normal plasma IgG level of 11.20 mg/ml

(range, 6.9 mg – 17.6 mg)[36], SVPE treated GBS patients received IgG dose of median 0.9 g/kg (range 0.6 g/kg – 1.3 g/kg).

Discussion

Principal findings

This study suggests SVPE may represent a safe and feasible alternative to conventional plasma exchange for patients with severe GBS in limited-resource settings. Of the 20 patients in this study, one (5%) experienced a SAE (severe sepsis due to probable CLABSI). The rate of SAE was not significantly higher than the hospital control group without GBS with a CVC, and no patients had a CVC-related thromboembolic event in patients with SVPE. We were able to remove the prespecified target volume (8 L) of plasma as the target primary endpoint of feasibility in 15/20 (75%) patients with GBS. Median plasma exchange volume and rate during SVPE were 8.4 L and 140 mL/kg, respectively. Minor adverse effects included transient hypotension during SVPE in 50% (10/20), minor haemorrhage from CVC insertion site in 50% (10/20), transfusion reaction to fresh frozen plasma in 20% (4/20), and hypo-albuminemia, anaemia and electrolyte imbalance in 20% (4/20) of patients. An improvement of at least one grade on the GBS disability score was observed for 14/20 (70%) patients at four weeks after the initiation of SVPE. No patients died.

Comparison with baseline hospital control patients and standard/modified PE

With respect to HAIs, no significant differences were observed in the frequency of CLABSI, severe sepsis, VAP or CAUTI between the SVPE-treated patients with GBS and 24 hospital control patients without GBS treated using a CVC in the same ICU or HDU (Fig. 2). However, antimicrobial agents were used more frequently, usually prophylactically, in the hospital control patients compared to the patients with GBS treated with SVPE ($p < 0.0001$; Fig. 2). The

probability of detecting microorganisms in clinical infections may have been reduced due to overzealous use of antibiotics in the hospital control patients. Early trials of PE in patients with GBS showed 34% of patients develop severe infections.[7 11] Subsequently, another large trial documented septicaemia in 19% of patients.[5] However, the rates of CLABSI were not reported.

A previous RCT on GBS from the US showed a beneficial effect with PE rate of 40-50 ml/kg/session, for 3 to 5 sessions in 7 to 14 days, which comes to a total PE volume of 120-250 ml/kg.[7] The first French RCT on adult GBS patients showed beneficial effect of 4 PE sessions [2 plasma volume (3.5 L) per PE session] over 8 days and in range, 6 – 12 L plasma was removed per patient.[4] Subsequent French RCT with PE dose escalation showed, 2 PE sessions [1.5 plasma volume per PE session] is beneficial in mild to moderate GBS cases but less effective than 4 PE sessions in severe GBS cases and 6 PE sessions are as effective as 4 PE sessions in severe cases of GBS.[5] In this RCT the exact total plasma volume exchanged per patient was not mentioned, but the authors indicated that the rate of plasma exchange was 40-ml/kg body weight per PE session. As to that a 60-70 kg person should have an exchange of 2.4 L-2.8 L per session and the therapeutic range of plasma volume to be exchanged would be 5.6 L to 11.2 L ml (2 to 4 PE sessions).

During the piloting of the SVPE procedure we assessed that removal of 1 L of patient plasma could be feasible in a day. Therefore we defined our target plasma volume of 8 L to be removed in 8 days. The median total PE volume and rate in SVPE was 8.4 L and 140 ml/kg, which is within the same range as in both the French and American RCT on PE for adult GBS patients. We were able to remove >120 mL/kg plasma in 80% of patients, which should provide a therapeutic effect.[37] Notably, the body weight of our patients may be lower than that of patients

in western countries. In addition, SVPE was complete within 8 days, shorter than the usual time required for a full session of PE (10 to 12 days).

Replacement fluid used in SVPE was FFP. We have several justifications in favour of using FFP instead of human albumin or other available colloidal solutions available in Bangladesh. First FFP is safe in terms of microbiological safety since stringent screening for viral and bacterial contamination was performed before infusion. Second, in contrast to human albumin and colloid solutions, FFP contains normal human IgG that could contribute beneficial immunotherapeutic effect in GBS and previously used as replacement fluid in large PE trials, quintessentially with the same volume (half the volume of replacement fluid) we used in SVPE.[4 5] SVPE treated GBS patients received approximately half the amount of IgG from the FFP used as replacement fluid compared to the total IVIg doses traditionally used in GBS (2gm/kg). Third, FFP contains all human plasma proteins that helps preservation of plasma colloid osmotic pressure and prevents formation of oedema and hypotension. Lastly FFP is much cheaper than commercial human albumin.

In each day three units of FFP were transfused as replacement fluid after the last session of SVPE and in the initial two to three sessions, normal saline was used as replacement fluid. This was done to achieve the maximum immunotherapeutic effect of FFP as SVPE was not resumed before the next day and the IgG in FFP remained in the circulation overnight for a longer period of time (10 to 12 hours). However due to long half life of IgG, substantial amount of IgG present in FFP were probably washed away due to repeated plasma removal both during SVPE and standard PE.

In GBS, treatment with modified methods of PE done previously, were device based and done on limited number of GBS patients. In one study on 25 GBS patients from India, daily removal of small volume of plasma (10-15 ml plasma/kg body weight) for duration of median 3 days using

traditional PE machine was shown to be clinically beneficial.[38] In another study from the same country, 12 GBS patients were treated with PE over 10 days using different PE-machine kit (REF627 kit from Haemonetics Corporation Limited on MCS+ machine) where authors claimed clinical improvement, however the main focus was on cost effectiveness and the total plasma volume exchanged per patient was not mentioned.[39] Nevertheless these methods are based on specific devices those are not in common practice, nor the trained personnel for these are available in the developing countries.

Important observations in terms of secondary endpoints were transient hypotension, transfusion reaction to FFP and minor bleeding through the CVC insertion site. Hypotension is a common complication during traditional PE that affects nearly half of patients.[5] Spells of hypotension during SVPE were more frequent during the three to four days after initiation of SVPE, and could be easily corrected by rapid infusion of 300-400 mL saline (Fig. 1). The hypotension could possibly be explained by hypovolemia due to drawing blood or as a result of the compromised autonomic nervous system in patients with GBS. As SVPE proceeded, hypotensive spells were encountered less frequently despite drawing the same volume of blood, which may in part be explained by adaptation of the vasomotor system or recovery from autonomic dysfunction. Minor bleeding through the CVC insertion site occurred in 50% of patients and could be controlled by applying a simple pressure pack over the CVC insertion site in most cases; mild prolonged PT was noted in 30% (3/10) patients. However, spontaneous bleeding usually occurs if the PT is more than 2.5 times prolonged and PC is < 0.50 lac/μL.[40] Movement of the limb where the CVC was placed may have caused traction on the CVC and contributed to local bleeding in the other seven patients. Haematuria is not uncommon in patients with a UTI, as may have occurred in one SVPE treated patient; traumatic traction of the urinary catheter may cause haematuria in two other catheterized SVPE-treated patient taking oral aspirin, who had haematuria and sterile urine.

We also monitored the major organ function and biochemical status of the patients treated with SVPE. No patients experienced hepatic or renal impairment. One patient developed anaemia and hypoalbuminemia; this patient had severe sepsis, a common cause of anaemia and hypoalbuminemia in critically ill patients admitted to an ICU (patient 11, Fig. 1). Electrolyte imbalances were detected in 15% of the SVPE-treated patients with GBS, and were mild, subclinical and easily corrected.

The median reported durations to recovery of independent walking in patients with GBS in large-scale RCTs after PE are 53, 52 and 70 days[4 5 7]; compared to 30 days in our patients treated with SVPE. Moreover, 60% of the patients with GBS treated with SVPE were able to walk independently at four weeks, whereas 20% of patients with GBS acquired independent walking ability at four weeks after traditional PE. However, these differences may possibly be due to the small sample size and variations in demographic and neurophysiological characteristics between cohorts. Finally, SVPE was completed in all 20 patients and no patients died.

Limitations of SVPE

SVPE is a time-consuming and labour-intensive procedure, which is a limitation. We used multiple thin-lumen tubing systems interconnected with a multichannel connecter device, which may increase the chance of blood coagulating within the tubing system. Coagulation may require manipulation or replacement of the tubing to ensure free flow of blood and saline. Such handling could increase the chance of microbial contamination. A single continuous wide-lumen tubing system (SVPE kit) could resolve this problem. Most importantly, personnel conducting the SVPE procedure should maintain proper aseptic technique, which can sometimes be challenging in developing countries. Furthermore, other adaptions such as provision of a larger blood bag or

increasing the number of days for SVPE could be considered to increase the plasma exchange rate.

Clinical implications and future research

Despite the limitations, our study showed SVPE is a safe and feasible treatment for GBS in a resource-limited setting where IVIg or PE are either unavailable or unaffordable. Specifically, the poorest 20% of the world's population (1.8 billion people) who typically earn less than 10 US$ per day and who are not covered by a national health insurance system may benefit. Considering the incidence of GBS is 2/100,000 in developing countries, approximately 40,000 patients could potentially benefit from SVPE every year, worldwide. In the future, a multicentre RCT is required to assess the clinical efficacy of SVPE for patients with GBS. If proven effective, SVPE could be an affordable and easily available alternative plasma exchange technique in low-income countries for patients with GBS and other disorders, who at present cannot afford standard PE due to its high cost and unavailability.

Declarations

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Transparency: The corresponding author affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1: Demographic and clinical characteristics of the 20 patients with GBS included in this small volume plasma exchange (SVPE) study at entry

Characteristic		Value
Demography		
Sex [males: females (ratio)]		13:7 (1.85)
Age (years) ¶		33 (18 - 55)
Body weight (kg) ¶		60 (50 -72)
Antecedent events ‡ (total)		18 (90%)
Diarrhoea		10 (50%)
Respiratory infection		5 (25%)
Fever		3 (15%)
Days from antecedent events to weakness ¶		7 (3 - 30)
Days between onset of weakness to admission ¶		7 (2-12)
Neurological deficits at entry		
Weakness in arms and legs		20 (100%)
Cranial nerve deficits		12 (60%)
Decreased deep tendon reflexes		20 (100%)
Sensory involvement		5 (25%)
GBS disability score §	4	19 (95%)
	5	1 (5 %)
Severity of weakness (MRC sum-score) ¶		20 (0-29)
Autonomic dysfunction		11 (55%)

¶ Median (range); † increased protein level (> 45 mg/dL) in combination with CSF cell count < 50/µL; CSF = cerebrospinal fluid; NCS = nerve conduction study; ‡ symptoms of an infection in the four weeks preceding the onset of weakness; § GBS disability score (0 - 6) = 0: healthy state; 1: minor symptoms and capable of running; 2: able to walk 10 meters or more without assistance but unable to run; 3: able to walk 10 meters across an open space with help; 4: bedridden or chair-bound; 5: requiring assisted ventilation for at least part of the day; 6: dead.

687 Table 2: Treatment characteristics and complications associated with SVPE in the 20 patients
688 with GBS

Characteristic/complication	Value
Treatment characteristics	
Number of sessions of SVPE per patient ¶	30 (24 - 42)
Volume of plasma removed per patient ¶	8.4 (6.3 – 9.6)
Plasma exchange rate (mL/kg) ¶	140 (110-175)
Time between hospital admission and SVPE (days) ¶	8 (5-10)
Time between onset of weakness and start of SVPE (days) ¶	8 (5-10)
Need to stop SVPE due to poor hemodynamic tolerance	0/20 (0%)
Need for blood transfusion for anaemia	1/20 (5%)
Reduction of anticoagulant drug dose for bleeding	3/20 (15%)
Temporary withdrawal of antiplatelet drug for bleeding	4/20 (20%)
Increased anticoagulant drug dose to continue SVPE	1/20 (5%)
CVC blockade/replacement	0/20 (0%)
Complications during SVPE	
Infection	
Leukocytosis	7/20 (35%)
CLABSI §	6.25
VAP §	136.4
CAUTI §	40
Severe sepsis	1/20 (5%)
Antimicrobial agents used	6/20 (30%)
Bleeding and coagulation	
Bleeding from CVC insertion site	10/20 (50%)
Bleeding from mucosal area	3/20 (15%)
Prolonged BT (BT > 10 min)	0/20 (0%)
Prolonged CT (CT > 15 min)	0/20 (0%)
Prolonged PT (PT > 14 sec) ¶	6/20 (30%) [15-19 sec]

Prolonged aPTT (aPTT > 40 sec) ¶	3/20 (15%) [51-240 sec]
Other complications	
Saline responsive hypotension	10/20 (50%)
Anaemia (Hb < 8 gm/L)	2/20 (10%)
Thrombocytopenia (PC < 1.5 lac/µL) ¶	6/20 (30%) [0.79-1.3 lac/µL]
Jaundice (serum bilirubin > 1.2 mg/dL)	0/20 (0%)
Renal impairment (serum creatinin > 1.2 mg/dL)	0/20 (0%)
Hyponatraemia (serum Na^+ < 135 mEq/L)	1/20 (5%) [126 mEq/L]
Hypokalaemia (serum K^+ < 3.5 mEq/L) ¶	3/20 (15%) [2.6-3.2 mEq/L]
Hypoalbuminemia (serum albumin > 35 gm/L) ¶	4/20 (20%) [26-32 gm/L]
Hypocalcaemia (serum Ca^+ < 2.2 mmol/L) ¶	3/20 (15%) [1.89-1.98 mmol/L]
Hypomagnesaemia (serum Mg^+ < 75 mEq/L) ¶	1/20 (5%) [73 mEq/L]
Hypersensitivity/transfusion reaction to FFP	4/20 (20%)

¶ Median (range); § rate per 1000 device days; CLABSI: central line-associated bloodstream infection; VAP: ventilator-associated pneumonia; CAUTI: catheter-associated urinary tract infection; CVC: central venous catheter; BT: bleeding time, CT: clotting time; PT: prothrombin time; APTT: activated partial thromboplastin time; FFP: fresh frozen plasma.

Table 3: Neurological outcomes of the 20 patients with GBS after SVPE

Clinical outcome	1 month	2 months	3 months	6 months
Cranial nerve involvement	7/20 (35%)	6/20 (30%)	4/20 (20%)	2/20 (10%)
Autonomic involvement	3/20 (15%)	3/20 (15%)	0/20 (0%)	0/20 (0%)
Sensory dysfunction	1/20 (5%)	1/20 (5%)	1/20 (5%)	1/20 (5%)
GBS disability score¶	0 = 0	0 = 1	0 = 1	0 = 2
	1 = 3	1 = 6	1 = 7	1 = 7
	2 = 9	2 = 6	2 = 6	2 = 5
	3 = 2	3 = 1	3 = 1	3 = 3
	4 = 3	4 = 5	4 = 5	4 = 3
	5 = 3	5 = 1	5 = 0	5 = 0
MRC sum score † ⁎	47 (0-60)	49 (0-60)	53 (6-60)	58 (22-60)
ONLS ‡ ⁎	4 (1-12)	3 (0-12)	3 (0-12)	2 (0-10)
R-ODS § ⁎	26 (0-41)	33 (0-45)	37 (0-45)	38 (0-46)

⁎ Median (range); ¶ GBS disability score (0 - 6) = 0: healthy state, 1: minor symptoms and capable of running, 2: able to walk 10 meters or more without assistance but unable to run, 3: able to walk 10 meters across an open space with help, 4: bedridden or chair-bound, 5: requiring assisted ventilation for at least part of the day, 6: dead; † MRC sum score: Medical Research Council sum score; ‡ ONLS: Overall Neuropathy Limitation Scale [22]; § R-ODS: Rash-built Overall Disability Score [23]

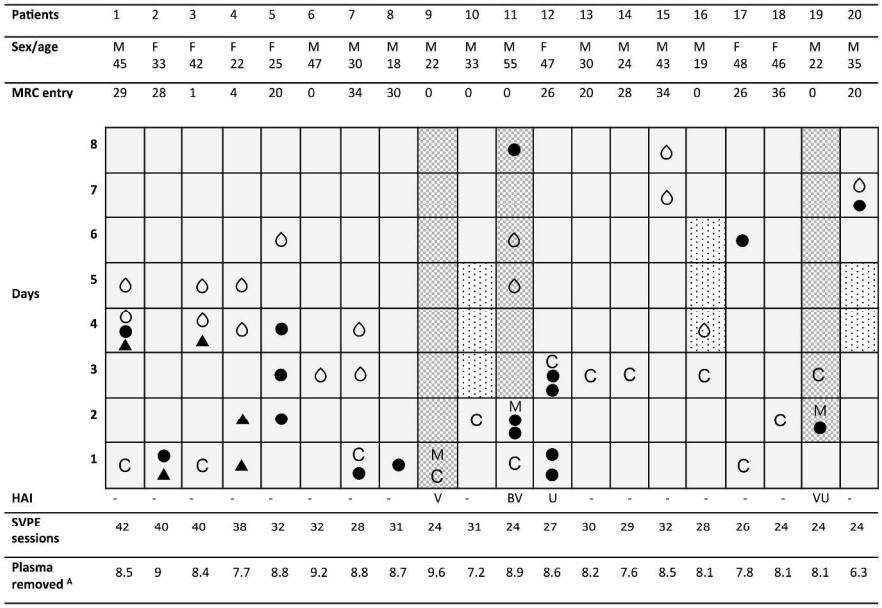
Figure 1: Feasibility of SVPE and associated complications for the 20 individual patients with GBS.

SVPE: small volume plasma exchange, HAI: hospital acquired infection, V: ventilator-associated pneumonia, B: central line-associated blood stream infection, U: catheter-associated urinary tract infection, [A] measured in litres, ●: spell of hypotension (systolic BP < 90 mm Hg), ◊: CVC insertion site bleeding, ▲: hypersensitivity to fresh frozen plasma, shaded squares: pyrexia due to bacterial infection, dotted squares: pyrexia due to suspected viral infection, M: onset of mechanical ventilation, C: urinary catheterization.

Figure 2: Hospital-acquired infections and use of antibiotics in the 20 patients with GBS receiving SVPE compared to the 24 hospital control patients without GBS treated in an ICU with a CVC who did not receive SVPE.

■ SVPE (n = 20): twenty patients with GBS aged ≥ 18-years-old who were bedbound (GBS disability score ≥ 4) received small volume plasma exchange (SVPE) within 2 weeks of the onset of weakness. ⊡ Non-SVPE (n=20): twenty-four patients aged ≥ 18-years-old with a diagnosis other than GBS who required a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units in the same period as the patients with GBS received SVPE; ∗ $p < 0.0001$.

Figure 3: Kaplan-Meier estimate (with 95% confidence limits) of the cumulative incidence of restoration of independent walking ability in patients with GBS treated with SVPE.



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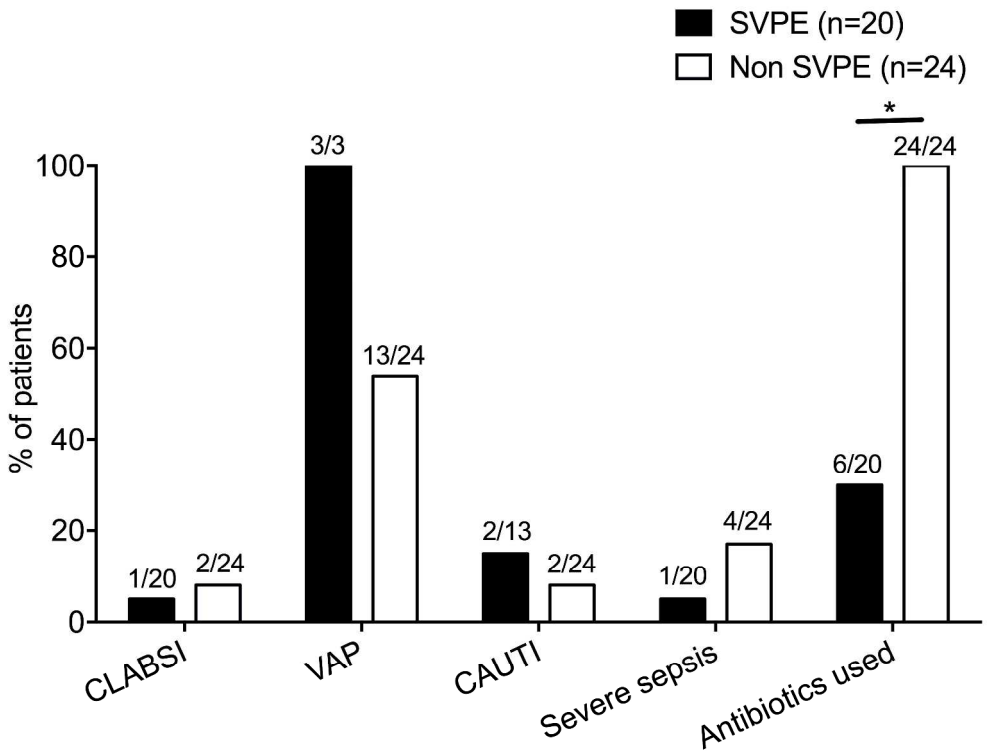

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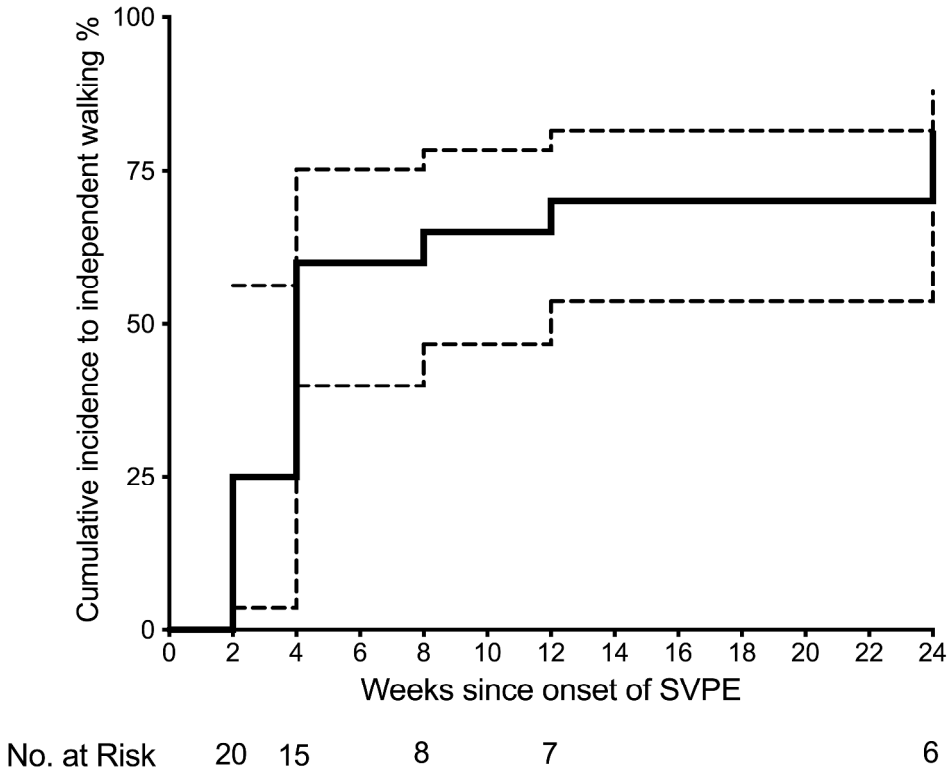
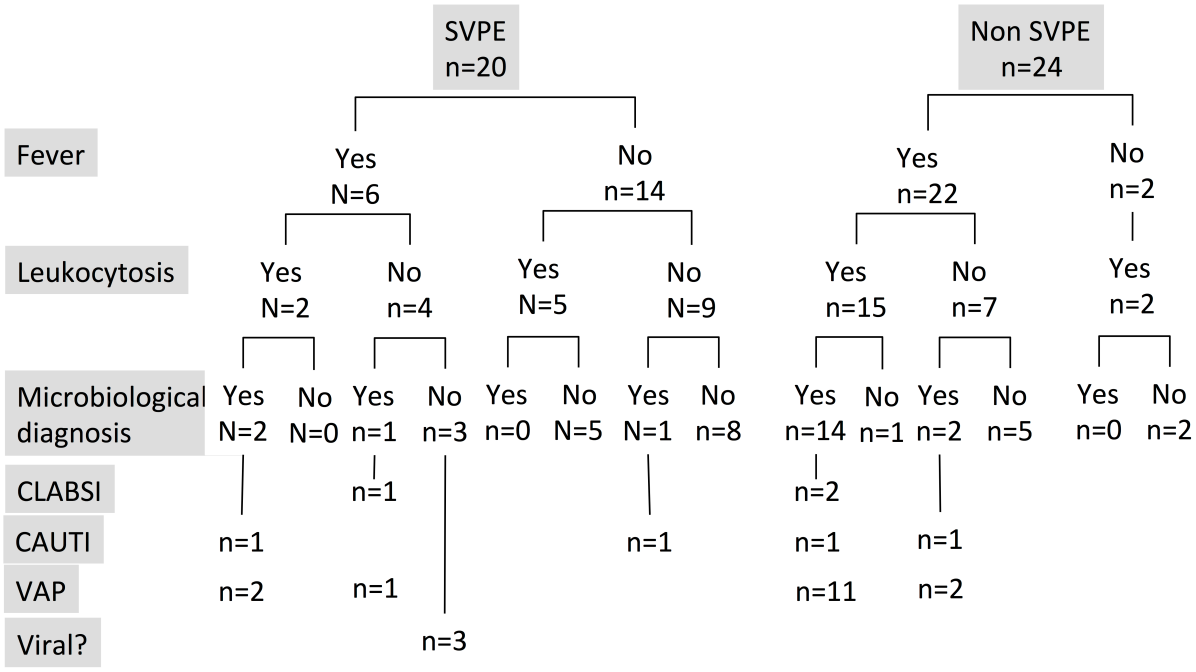


Figure 3: Kaplan-Meier estimate (with 95% confidence limits) of the cumulative incidence of restoration of independent walking ability in patients with GBS treated with SVPE.

Supplementary Figure: Hospital-acquired infections in the 20 patients with GBS treated with SVPE and the 24-hospital control patients without GBS.



SVPE: small volume plasma exchange, CLABSI: central line-associated blood stream infection, CAUTI: catheter-associated urinary tract infection, VAP: ventilator-associated pneumonia.

2017 CONSORT checklist of information to include when reporting a randomized trial assessing nonpharmacologic treatments (NPTs)*. Modifications of the extension appear in italics and blue.

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
Title and abstract					
	1a	Identification as a randomized trial in the title	NA (Non-randomized)		
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3, 4, 5	Refer to CONSORT extension for abstracts for NPT trials	3, 4, 5
Introduction					
Background and objectives	2a	Scientific background and explanation of rationale	6		
	2b	Specific objectives or hypotheses	6, 7		
Methods					
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7	When applicable, how care providers were allocated to each trial group	NA
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	No changes to methods after trial commencement		
Participants	4a	Eligibility criteria for participants	7, 8	When applicable, eligibility criteria for centers and for care providers	NA
	4b	Settings and locations where the data were collected	7		
Interventions†	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7, 8	Precise details of both the experimental treatment and comparator	7, 8
	5a			Description of the different components of the interventions and, when applicable, description of the procedure for tailoring the interventions to individual participants.	9
	5b			Details of whether and how the interventions were standardized.	8, 9

Cite as: *Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40–7.*

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
	5c.			Details of whether and how adherence of care providers to the protocol was assessed or enhanced	8, 9
	5d			Details of whether and how adherence of participants to interventions was assessed or enhanced	NA
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9		
	6b	Any changes to trial outcomes after the trial commenced, with reasons	No changes to trial outcomes after the trial commenced		
Sample size	7a	How sample size was determined	9	When applicable, details of whether and how the clustering by care providers or centers was addressed	NA
	7b	When applicable, explanation of any interim analyses and stopping guidelines	10		
Randomization:					
- Sequence generation	8a	Method used to generate the random allocation sequence	NA (Non-randomized)		
	8b	Type of randomization; details of any restriction (such as blocking and block size)	NA (Non-randomized)		
- Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	NA (Non-randomized)		
- Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	NA (Non-randomized)		
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Blinding was not possible	If done, who was blinded after assignment to interventions (e.g., participants, care providers, those administering co-interventions, those assessing outcomes) and how	Blinding was not possible

Cite as: *Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40–7.*

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
	11b	If relevant, description of the similarity of interventions	7, 8		
	11c			If blinding was not possible, description of any attempts to limit bias	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10	When applicable, details of whether and how the clustering by care providers or centers was addressed	NA
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NA		
Results					
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	11	The number of care providers or centers performing the intervention in each group and the number of patients treated by each care provider or in each center	Single center study
	13b	For each group, losses and exclusions after randomization, together with reasons	No losses and exclusions after inclusion		
	13c			For each group, the delay between randomization and the initiation of the intervention	11
	new			Details of the experimental treatment and comparator as they were implemented	11-16
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7		
	14b	Why the trial ended or was stopped	NA (Trial completed)		
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1	When applicable, a description of care providers (case volume, qualification, expertise, etc.) and centers (volume) in each group.	NA
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11-12		

Cite as: *Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40–7.*

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12-16		
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA		
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	15		
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12-15		
Discussion					
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	20-21	In addition, take into account the choice of the comparator, lack of or partial blinding, and unequal expertise of care providers or centers in each group	NA
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	16-20	Generalizability (external validity) of the trial findings according to the intervention, comparators, patients, and care providers and centers involved in the trial	16-20
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16-20		
Other information					
Registration	23	Registration number and name of trial registry	4		
Protocol	24	Where the full trial protocol can be accessed, if available	Manuscript reference no: 17		
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	22		

**Additions or modifications to the 2010 CONSORT checklist. CONSORT = Consolidated Standards of Reporting Trials*
†The items 5, 5a, 5b, 5c, 5d are consistent with the Template for Intervention Description and Replication (TIDieR) checklist

Cite as: *Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40–7.*

Table: Required documents of the safety and feasibility study of the small volume plasma exchange (SVPE) for Guillain-Barré syndrome patients for the World Health Organization Trial Registration Data Set

	Item/Label	Description
1	Primary Registry and Trial **Identifying** Number	Clinicaltrials.gov NCT02780570
2	Date of Registration in Primary Registry	May 23, 2016
3	Secondary Identifying Numbers	International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) Protocol Number: PR-15086, Version no. 3, Date: 09/12/2015
4	Source(s) of Monetary or Material Support	GBS/CIDP Foundation International Fondation Mérieux: (Small Grants Program 2015)
5	Primary Sponsor	GBS/CIDP Foundation International
6	Secondary Sponsor(s)	Fondation Mérieux: (Small Grants Program 2014)
7	Contact for public queries	MD. BADRUL ISLAM Email: bislamdmch@gmail.com Telephone no: +880 1712 89 0172 Postal address: Dr. Badrul Islam

		Research trainee and PhD Fellow Laboratory Sciences and Services Division (LSSD) Icddr,b Dhaka, Bangladesh
8	Contact for scientific queries	MD. BADRUL ISLAM Principal Investigator (PI) Email: bislamdmch@gmail.com Telephone no: +880 1712 89 0172 Postal address: Dr. Badrul Islam Research trainee and PhD Fellow Laboratory Sciences and Services Division (LSSD) Icddr,b Dhaka, Bangladesh
9	Public title	Small volume plasma exchange for Guillain-Barré syndrome
10	Scientific title	Small volume plasma exchange for Guillain-Barré syndrome in low-income countries: a safety and feasibility study
11	Countries of Recruitment	Bangladesh
12	Health condition(s) or problem(s) studied	Guillain-Barré syndrome (GBS)
13	Interventions	*Small Volume Plasma Exchange (SVPE)* A loading dose of low-molecular weight heparin (1.5 mg/kg) will be given subcutaneously at least two hours

before initiation of SVPE; the same dose will be administered once daily or divided into two equal doses daily for eight days or until SVPE is completed. Whole blood (7 mL/kg body weight) will be drawn from the central venous catheter into the blood transfusion bag in each session. The blood bag will be hung beside the patient for 2.5 h on a saline stand and left uninterrupted to allow plasma and blood cells to separate. The blood cells will be infused back into the patient and plasma will be discarded and replaced with fresh frozen plasma and colloid solution alternately (in equal volumes) via the closed-circuit SVPE kit illustrated in. In case of excessive clotting (bleeding time reduction of > 50% of baseline for that patient), aspirin (600 mg) will be administered orally at least two hours before the next SVPE session and continued thereafter at 150 mg orally/day until SVPE is completed. One blood bag will be used each day, with a total of six sessions/day. A total of 48 sessions will be performed over eight days, removing approximately 8000 mL plasma in total.

Central venous catheterized patients without GBS

To compare the safety of SVPE in patients with GBS in the context of the background risk of central line-associated blood stream infection (CLABSI) at the study intensive care (ICU) and high-dependency care (HDU) units, the incidence of CLABSI will be assessed in a control group of adult patients with a diagnosis other than GBS admitted to the same ICU and HDU units in the same period of time the patients with GBS will be enrolled for SVPE. We will assess the rate of CLABSI in

		patients aged ≥ 18-years-old requiring a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units.
14	Key Inclusion and Exclusion Criteria	*Inclusion criteria for SVPE in GBS patients* 1. Patients aged ≥ 18-years-old fulfilling the diagnostic criteria for GBS of the National Institute of Neurological and Communicative Disorders and Stroke (NINDS) 2. Unable to walk unaided for more than 10 meters (GBS disability score ≥ 3) 3. Presented within 2 weeks of the onset of weakness 4. Unable to afford standard treatment with IVIg or PE. *Exclusion criteria for SVPE in GBS patients* 1. Patients with severe or terminal concomitant illness 2. Evidence of healthcare-associated infection on admission (except for aspiration pneumonia) 3. Previous history of severe allergic reaction to properly matched blood products and pregnant women will be excluded from the study. *Inclusion criteria for patients without GBS* 1. Patients aged ≥ 18-years-old 2. Requiring a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units in the same period of time the patients with GBS enrolled for SVPE. *Exclusion criteria for patients without GBS*

		1. Patients with healthcare-associated infection present on admission (except aspiration pneumonia) 2. Pregnant women
15	Study type	*Type of the study*: Interventional *Method of allocation:* Non-randomized *Masking:* Non-masked *Assignment:* Parallel arm • SVPE in patients with GBS • Rate of CLABSI in patients without GBS *Purpose:* Safety and feasibility of SVPE
16	Date of first enrolment	February 20, 2016
17	Target sample size	SVPE in patients with GBS = 20 Rate of CLABSI in patients without GBS = ≥ 20
18	Recruitment status	Completed: • Twenty cases of GBS have been successfully treated with SVPE and 24 control cases without GBS have been recruited.
19	Primary Outcome(s)	*Primary outcome of safety*: 1. Number of patients with GBS treated with SVPE developing severe sepsis or septic shock due to central line associated blood stream infection (CLABSI) as per standard guideline (Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central line-associated Bloodstream Infection); CDC Device-associated Module, BSI. January 2017) 2. Occurrence of venous thrombosis in the limb

		where the CVC is placed. Venous thrombosis will be assessed according to Wells criteria (*Philip S. Wells et al. Evaluation of d -Dimer in the Diagnosis of Suspected Deep-Vein Thrombosis; N Engl J Med 2003;349:1227-35*) *Primary outcome of feasibility*: 1. Ability to remove at least eight litres of plasma by SVPE over eight days.
20	Secondary Outcome(s)	*Secondary outcome of safety*: 2. Relative risk of CLABSI due to SVPE compared to CLABSI in control patients without GBS treated using a CVC 3. Hemodynamic instability during the SVPE procedure (variations in systolic blood pressure greater than 30 mmHg or sudden bradycardia involving a reduction in heart rate by more than 20 beats per min within 30 min of starting SVPE or an increase in heart rate above 120 beats per min) 4. Development of anaemia (Hb <7 gm/dL) or serious haemorrhage requiring blood transfusion. *Secondary outcome of feasibility*: 1. Rate of CVC occlusion during the SVPE procedure 2. The healthcare personnel's acceptability and

		satisfaction with the SVPE procedure and any unanticipated events compromising the SVPE procedure as assessed using a standard questionnaire. 3. Neurological outcome will be assessed in terms of improvement in GBS disability score and MRC sum score at discharge and up to 4 weeks after entry.

BMJ Open

Small volume plasma exchange for Guillain-Barré syndrome in resource-limited settings: a phase II safety and feasibility study

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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Medical management
Keywords:	Guillain-Barré syndrome, Small volume plasma exchange, Safety, Feasibility

Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.

SUPPLEMENTARY VIDEO.mp4

Title:

Small volume plasma exchange for Guillain-Barré syndrome in resource-limited settings: a phase II safety and feasibility study

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Word count: 5087 (Excluding abstract, reference, table and figures)

ABSTRACT

OBJECTIVE

To assess the safety and feasibility of small volume plasma exchange (SVPE) for Guillain-Barré syndrome (GBS) patients.

DESIGN

Non-randomized, single arm, interventional trial.

SETTING

National Institute of Neurosciences and Hospital, Dhaka, Bangladesh.

PARTICIPANTS

Twenty adult (>18 years) patients with GBS presented within 2 weeks of onset of weakness who were unable to walk unaided for more than 10 meters.

INTERVENTIONS

SVPE involves blood cell sedimentation in a blood bag and removal of supernatant plasma after blood cells are re-transfused. This procedure was repeated three to six times a day, for eight consecutive days. Fresh frozen plasma (FFP) and normal saline were used as replacement fluid.

OUTCOME MEASURES

Serious adverse events (SAE) were defined as severe sepsis and deep venous thrombosis related to the central vein catheter (CVC) used during SVPE. SVPE was considered safe if less than 5/20 patients experienced a SAE, and feasible if 8 L plasma could be removed within 8 days in at least 15/20 patients.

RESULTS

Median patient age 33 years (IQR 23-46; range 18-55); 13 (65%) were male. Median MRC sum score was 20 (IQR 0-29; range 0-36); three (15%) patients required mechanical ventilation. One patient developed SAE (severe sepsis, possibly related to CVC). The median plasma volume exchanged was 140 mL/kg (range 110-175) and removal of 8 L plasma was possible in 15 (75%)

patients. Patients received a median 1g/kg IgG via FFP although a substantial proportion of IgG was probably removed again by the SVPE sessions. GBS disability score improved by at least one grade in 14 (70%) patients four weeks after SVPE started. No patients died.

CONCLUSION

SVPE seems a safe and feasible alternative treatment to standard PE or IVIg for GBS; further studies of clinical efficacy in low-resource developing countries are warranted.

TRIAL REGISTRATION

Clinicaltrials.gov NCT02780570 on May 23, 2016

Strength and limitations of the study:

1. The strength of this study underlies the novel and simple technique of SVPE, which is much less expensive than conventional immunotherapies [plasma exchange (PE) and intravenous immunoglobulin (IVIg)]
2. SVPE is corroborated as safe and feasible for the first time in a prospective and standardized cohort of patients with Guillain-Barré syndrome (GBS).
3. The intrinsic limitations of this study are its non-randomized, single arm nature, which is conducted in a single center with a limited sample size of GBS patients. The volume exchanged was at the lower range compared to previous PE studies conducted in GBS.
4. Clinical efficacy of SVPE on patients with GBS was a secondary end-point assessment and therefore deserves a randomized controlled trial in future to assess the clinical efficacy of SVPE for the patients with GBS.

Introduction

Guillain-Barré syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy with a yearly incidence of 1.2 to 2.3 cases per 100,000 per year.[1] GBS is characterized by rapidly progressive limb weakness and, in a proportion of cases, respiratory failure (25%) or severe autonomic dysfunction (10%). Plasma exchange (PE) was the first treatment proven to be effective for GBS, if given within 4 weeks of the onset of weakness.[2-11] Conventionally for GBS patients, three to five plasma exchange sessions are done in alternate days within a span of 7 to 14 days targeting a plasma exchange rate of 120 - 200 ml/kg (40-50ml/kg/day).[7]. Later studies showed treatment with intravenous immunoglobulin (IVIg) (0.4 g/kg per day for 5 days) has a similar efficacy as PE in patients with GBS who are unable to walk, if started within 2 weeks of the onset of weakness.[12 13]

Unfortunately, most patients in low-income countries cannot afford expensive treatment with either PE or IVIg.[14] In Bangladesh, a full course of IVIg for a 60 kg adult costs approximately 12,000-16,000 US$ and treatment with conventional PE for 5 days costs approximately 4,500-5,000 US$. The mean income in Bangladesh was 4 US$ per day in 2016 (World Bank and Bangladesh Bureau of Statistics 2016); IVIg and PE cost the equivalent of 3,000 and 1,250 mean income days, respectively. At present, the majority (92%) of patients with GBS in Bangladesh receive supportive care only.[14] In addition, mobile PE equipment is not available in Bangladesh; therefore, patients admitted to the intensive care unit (ICU) cannot receive PE. We previously reported the mortality rates for GBS in Bangladesh range from 12 to 14% and observed 29% of patients with GBS in Bangladesh are unable to walk at 6 months after onset; these poor outcomes are undoubtedly due to the low rates of specific treatment with PE or IVIg.[15 16]

Small volume plasma exchange (SVPE) may represent a cheap, effective alternative treatment for GBS. SVPE is based on the same principle as conventional PE (selective removal of plasma) but uses a novel, simple technique with much lower costs (approximately 500 US$). The current non-randomized trial was designed to investigate the safety and feasibility of SVPE in 20 patients with GBS admitted to the National Institute of Neurosciences Hospital in Dhaka, Bangladesh.

Methods/Design

Study design

For this non-randomized, single arm, interventional safety and feasibility trial, 20 adult patients with GBS were enrolled between March 2016 and December 2016 for SVPE at the National Institute of Neurosciences and Hospital (NINS), Dhaka, Bangladesh. A detailed study protocol was published previously and includes definitions of all variables used in this study.[17]

Four to six daily sessions of whole blood sedimentation and removal of supernatant plasma after re-transfusion of the sedimented blood cells was planned for the 20 patients with GBS, with a target of removing an overall volume of at least 8 litres (L) of plasma over a total of 8 days.[17] (See supplementary video for SVPE procedure)

Patients with GBS were monitored according to a standard protocol throughout the course of SVPE until the second day after withdrawal of the central venous catheter (CVC) in order to assess predefined measures of safety and feasibility and followed up for six months to assess neurological outcome. The protocol was reviewed and approved by the institutional research and ethics review committees at the icddr,b and registered at clinicaltrials.gov (NCT02780570).[17] All patients provided written informed consent to participate in this study.

Patient and Public Involvement

Patients and or public were not involved either in the development of the research question, study design and outcome measure or recruitment to and conduct of the study.

Inclusion and exclusion criteria for patients with GBS

Patients aged ≥ 18-years-old fulfilling the diagnostic criteria for GBS of the National Institute of Neurological and Communicative Disorders and Stroke (NINDS)[18] were enrolled, provided they were unable to walk unaided for more than 10 meters (GBS disability score ≥ 3), presented within 2 weeks of the onset of weakness, and were unable to afford standard treatment with IVIg or PE. Patients with concomitant severe or terminal illnesses, evidence of healthcare-associated infection (HAI) on admission (except for aspiration pneumonia), a previous history of severe allergic reactions to properly matched blood products, and pregnant women were excluded from the study.

Control cohort

To compare the safety of SVPE in patients with GBS in the context of the background risk of central line-associated blood stream infection (CLABSI) at our institution, we prospectively assessed the incidence of CLABSI in a hospital control group of 24 adult patients without GBS receiving neurocritical care. Hospital controls were eligible based on the following characteristics: ≥ 18-years-old, a neurological diagnosis other than GBS, and a CVC placed for > 2 and ≤ 8 calendar days after admission to the same ICU or HDU unit as the SVPE-treated patients. Patients with a HAI (except aspiration pneumonia) and pregnant women were excluded from the control group.

Primary and secondary outcome measures

The primary outcome measures of safety were the number of patients with GBS treated with SVPE who developed either severe sepsis or septic shock due to CLABSI[19] and the occurrence of venous thrombosis in the limb where the CVC was placed. The primary outcome measure of feasibility was the ability to remove at least 8 L of plasma over 8 days.

The secondary outcome measures of the safety of SVPE were the relative risk of CLABSI due to SVPE (compared to CLABSI in the hospital control group without GBS), hemodynamic instability during the SVPE procedure, and development of anaemia (Hb < 8 gm/dL) or any catheter-related haemorrhage requiring a blood transfusion.

The secondary outcome measure of feasibility of SVPE was the rate of CVC occlusion during the SVPE procedure. In addition, neurological outcome was assessed using the GBS disability score[20], MRC sum score[21], Overall Neuropathy Limitation Scale (ONLS)[22] and Rasch-built Overall Disability Scale (R-ODS)[23] at 1st, 2nd , 3rd , and 6th months from the start of SVPE.

Procedure safety documentation and cost of SVPE

Strict aseptic procedures were followed to prevent CLABSI.[24-26] SVPE was documented in terms of the duration and amount of plasma removed in each session, and the type and volume of replacement fluid and fresh frozen plasma (FFP) used. Throughout the procedure, the haemodynamic, haematological, biochemical, coagulation and infection profiles of the SVPE-treated patients were monitored according to the protocol.[17] Screening for hepatitis B and C viruses, human immunodeficiency virus (HIV) and syphilis were performed as patient baseline assessments, and also on donor FFP before administration. CLABSI, primary and secondary bloodstream infections[19], catheter-associated urinary tract infection (CAUTI)[27], ventilator-associated pneumonia (VAP)[28] and other HAI[29 30] were documented in the SVPE-treated patients with GBS and the hospital control group. Expenditure for the full course of SVPE will be

approximately 500 US$ [fresh frozen plasma (24 bags) = 240 US$, blood bag and saline sets: 40 US$, low molecular weight heparin: 110 US$, routine investigation: 50 US$, saline: 10 US$, CV catheter: 40 US$ = total 490 US$].

Sample size

This safety and feasibility study enrolled 20 patients with GBS for SVPE. We could not perform a formal power calculation for this safety and feasibility study. The sample size was based on previous pilot studies conducted in GBS.[31 32] The baseline rate of CLABSI was measured in the hospital control group of 24 patients without GBS admitted to the same study facility who required a CVC for at least 8 days during the study period.

Stopping rules for the trial based on safety and feasibility

Decision to stop the SVPE trial was designated using a Bayesian approach.[33-35] Accordingly, a predictive success rate of 75% was predefined for the SVPE procedure. If more than 5 of 20 patients experienced an SAE, or if it appeared impossible to remove at least 8 L of plasma over 8 days in at least 15 of 20 patients, the procedure was considered unsafe or unfeasible.

Statistical analysis

The rate of HAIs (CLABSI, VAP and CAUTI) per 1000 device days were calculated by dividing the number of each HAI during the study period by the number of device days and multiplying the result by 1000. The infection safety profile for SVPE was assessed by calculating the standardized infection ratio to define the risk of HAIs in patients with GBS treated with SVPE. The standardised infection ratio (SIR) was calculated by dividing the number of observed HAI by the number of HAI predicted (i.e., the infection rate in the control

group). The predicted HAI rate was calculated using the rates of HAI in the hospital control group of patients without GBS during the study period. Percentage values were compared using the Chi-square test or Fisher's exact test (two-tailed) and median values, the Mann-Whitney U-test using SPSS 22 software (IBM SPSS Statistics for Windows Version 22.0., IBM Corp., Armonk, NY, USA). Analyses were performed on an intention-to treat basis. All *P*-values reported are two-sided; $p < 0.05$ was considered significant.

Results

Patients and hospital controls

The demographic and clinical characteristics of the 20 patients with GBS are given in Table 1. The median age of the patients with GBS was 33 years (range; 18-55); median body weight was 60 kg (IQR, 55-65 kg; range, 50-72 kg) and 13 (65%) patients were male (Fig. 1). On admission and before the start of SVPE, all 20 patients with GBS were unable to walk independently (GBS disability score, 4). One patient required mechanical ventilation from the second day after the onset of weakness; SVPE was started on the fourth day of mechanical ventilation (patient 9, Fig. 1). Two of the 19 patients who did not require mechanical ventilation at the start of the study required mechanical ventilation on the second day after initiation of SVPE (patients 11 and 19, 11 and 2 days after the onset of weakness, respectively; Fig. 1). The median MRC sum score for the limb muscles in all 20 patients was 20 (IQR: 0-29; range: 0-36; Fig. 1). Symptoms of a preceding infection in the 4 weeks before the onset of weakness were present in 18 (90%) patients with GBS, of whom 10 (50%) had diarrhoea. Median duration from admission to start of SVPE was two days (IQR, 2-3 days; range, 0-7 days). Median duration to nadir from the onset of weakness was five days (range, 1-13 days). Electrodiagnostic nerve conduction studies indicated 15 (75%) patients had an axonal subtype and 5 (25%) patients had a demyelinating subtype of GBS. Median duration from onset of weakness to NCS examination was 10 days (range, 4-16

days). All patients had albuminocytologic dissociation; median CSF protein was 166 mg/dL (range 117-253 mg/dL). Median duration from onset of weakness to CSF examination was 11 days (range, 4-17 days).

Median age of the 24 hospital control patients without GBS was 44 years (IQR, 25-57; range; 18-74); 10 (42%) were male. Age and gender distribution were not significantly different compared to the 20 patients with GBS ($p = 0.2155$, $p = 0.1434$, respectively). The diagnoses for these 24 patients were: brain tumour ($n = 5$), transverse myelitis ($n = 5$), head trauma after road traffic accident ($n = 3$), viral meningoencephalitis ($n = 2$), myasthenia gravis ($n = 2$), compressive cervical myelopathy ($n = 2$), cerebrovascular accident ($n = 2$), motor neuron disease ($n = 1$), electrolyte imbalance ($n = 1$) and status epilepticus ($n = 1$).

Primary endpoints

One patient with GBS treated with SVPE developed severe sepsis, possibly due to SVPE-related CLABSI (SVPE window-period blood culture revealed methicillin-resistant *Staphylococcus aureus*). This patient required intravenous fluid, noradrenalin infusion and intravenous antibiotics, but eventually improved (patient 11, Fig. 1). This patient also had signs and symptoms suggestive of aspiration pneumonia and VAP; *Streptococcus spp.* was isolated from pulmonary aspirates. Further laboratory results revealed dys-electrolytemia, anaemia and hypo-albuminemia. No patients experienced deep vein thrombosis due to the CVC for SVPE. Fifteen (75%) of the 20 patients met the primary endpoint of feasibility, defined as the ability to remove at least 8 L of plasma in eight days. The median volume of plasma removed was 8.5 L (IQR, 7.9-8.8 L; range, 6.3-9.6 L; Fig. 1). The median plasma exchange rate was 140 mL/kg bodyweight (IQR, 125-155 mL/kg; range, 110-175 mL/kg) over 8 days and 16 (80%) patients had a plasma exchange rate > 120 mL/kg (Table 2).

Secondary endpoints

Infections among SVPE-treated patients with GBS and hospital controls

Among the 20 patients with GBS treated with SVPE, six (30%) had fever during SVPE (Fig. 1, Supplementary Figure 1), including 2 (10%) patients with leucocytosis who were diagnosed with HAI (VAP and CAUTI in one patient; VAP in one patient). In three out of four (20%) patients with fever without leucocytosis, fever subsided within two to three days without antimicrobial therapy (Fig. 1). The remaining patient with pyrexia without leucocytosis had microbiological evidence of both CLABSI and VAP (patient 11, Fig. 1). In all other 14 patients with GBS, no fever was documented during the course of SVPE until the tenth day of SVPE (second day after removal of the CVC for SVPE). Five of these 14 patients had leucocytosis, but no site-specific HAI could be detected. However, one of the nine patients without fever but leucocytosis fulfilled the criteria for CAUTI (patient 12, Fig. 1). All three patients who required mechanical ventilation subsequently developed VAP; two of the 13 patients who required a urinary catheter developed a CAUTI (patient 11, Fig. 1). No patients died during the 6 months follow-up.

All 24-hospital control patients without GBS required mechanical ventilation and an indwelling urinary catheter. Of these patients, 22 (92%) patients had fever, of whom 15 (63%) had leucocytosis; a diagnosis of a specific HAI could be made 14 of these 15 patients (CLABSI in two, CAUTI in one, VAP in 11) and four (17%) fulfilled the criteria for severe sepsis (Supplementary Figure 1). Seven (29%) of the 24 hospital control patients had fever without leucocytosis. In two of these seven patients, a specific HAI was diagnosed (CAUTI and VAP in one, and VAP in one). In two hospital control patients, no fever was documented until day 10 after first placement of the CVC, but leucocytosis was present and no site-specific HAI could be detected (Supplementary Figure 1).

The rates of CLABSI, CAUTI and VAP per 1000 device days in the SVPE-treated patients with GBS were 6.25, 19.2 and 40 compared to 10.4, 10.4 and 67.7 for the hospital control patients without GBS, respectively. The relative risks of CLABSI, CAUTI and VAP associated with SVPE were 0.6, 1.2 and 1.8, respectively, compared to hospital control patients. The rates of CLABSI, CAUTI and VAP were comparable between SVPE-treated patients with GBS and hospital control patients ($p > 0.05$). Antimicrobial agents were used more frequently in the hospital control patients ($p < 0.0001$; Fig. 2). The standardised infection ratios for CLABSI, CAUTI and VAP for SVPE-treated patients with GBS were 0.6, 1.8 and 1.9, respectively.

Other secondary endpoints

Ten (50%) of the 20 patients treated with SVPE experienced transient hypotension during SVPE, which was corrected by infusion of 200-300 mL crystalloid saline (Fig. 1). Minor bleeding through the CVC insertion site (excluding at the time of insertion) was observed in 10/20 patients (50%; Fig. 1); these bleeds required a pressure pack. Reduction of the anticoagulant dose along with a pressure pack was required in 3/20 patients, who all had a prolonged prothrombin time (PT). Three patients had single episode of haemorrhage through the urinary catheter: one was diagnosed with a CAUTI with normal coagulation profile, one had a prolonged PT, the other had sterile haematuria with normal PT. Overall, PT and activated partial thromboplastin time (aPTT) were prolonged in 4/20 patients and only PT was prolonged in 2/20 patients. Clotting time and bleeding time were not prolonged in any patient. One patient developed anaemia (haemoglobin, 8 gm/L) at the end of SVPE; this patient also had severe sepsis and required one unit of blood transfusion (patient 11, Fig. 1). CVC blockages were not observed in any SVPE-treated patients with GBS. One patient with increased clotting tendency who required an increased dose of low molecular weight heparin had shortened clotting time (CT) (< 50% of upper limit of normal), though PT was normal (patient 10, Fig. 1).

The neurological outcomes of the SVPE-treated patients with GBS at six months in terms of neurological scores are given in Table 3. Median time to recover the ability to walk unaided was 4 weeks (Fig. 3). Fourteen (70%) of the 20 patients had an improvement in GBS disability score of one or more grades at four weeks after the onset of SVPE. At one month, 12 patients (60%) were able to walk unaided, two patients (10%) were able to walk aided and six (30%) patients were bedbound, of whom three still required mechanical ventilation. At three months, 14 (70%) patients were able to walk unaided, one (5%) could walk with aid and five (25%) patients were bedbound. At six months, 14 (70%) patients were able to walk unaided, three (5%) could walk with aid and three (15%) remained bedbound (Table 3).

Other relevant clinical and laboratory findings

Allergic/transfusion reaction to FFP was observed in four patients with GBS treated with SVPE (Fig. 1). These transfusion reactions presented as an itchy erythematous skin rash (three patients), fever (two patients), hypotension (one patient) following transfusion of FFP; all of these reactions were managed with oral antihistamine (and intravenous saline in one patient) without further complications.

The other documented haematological and biochemical abnormalities were hypo-albuminemia (n = 4), thrombocytopenia (n = 6), hyponatraemia (n = 1), hypokalaemia (n = 3), hypomagnesaemia (n = 1), hypocalcaemia (n = 3); (Table 2).

Immunoglobulin dosage admitted by FFP

During SVPE the median volume of FFP administered per GBS patient as replacement fluid was 6000 ml (range, 5000 ml to 6000 ml). Considering the normal plasma IgG level of 11.20 mg/ml

(range, 6.9 mg – 17.6 mg)[36], SVPE treated GBS patients received IgG dose of median 0.9 g/kg (range 0.6 g/kg – 1.3 g/kg).

Discussion

Principal findings

This study suggests SVPE may represent a safe and feasible alternative to conventional plasma exchange for patients with severe GBS in limited-resource settings. Of the 20 patients in this study, one (5%) experienced a SAE (severe sepsis due to probable CLABSI). The rate of SAE was not significantly higher than the hospital control group without GBS with a CVC, and no patients had a CVC-related thromboembolic event in patients with SVPE. We were able to remove the prespecified target volume (8 L) of plasma as the target primary endpoint of feasibility in 15/20 (75%) patients with GBS. Median plasma exchange volume and rate during SVPE were 8.4 L and 140 mL/kg, respectively. Minor adverse effects included transient hypotension during SVPE in 50% (10/20), minor haemorrhage from CVC insertion site in 50% (10/20), transfusion reaction to FFP in 20% (4/20), and hypo-albuminemia, anaemia and electrolyte imbalance in 20% (4/20) of patients. An improvement of at least one grade on the GBS disability score was observed for 14/20 (70%) patients at four weeks after the initiation of SVPE. No patients died.

Comparison with baseline hospital control patients and standard/modified PE

With respect to HAIs, no significant differences were observed in the frequency of CLABSI, severe sepsis, VAP or CAUTI between the SVPE-treated patients with GBS and 24 hospital control patients without GBS treated using a CVC in the same ICU or HDU (Fig. 2). However, antimicrobial agents were used more frequently, usually prophylactically, in the hospital control patients compared to the patients with GBS treated with SVPE ($p < 0.0001$; Fig. 2). The

probability of detecting microorganisms in clinical infections may have been reduced due to overzealous use of antibiotics in the hospital control patients. Early trials of PE in patients with GBS showed 34% of patients develop severe infections.[7 11] Subsequently, another large trial documented septicaemia in 19% of patients.[5] However, the rates of CLABSI were not reported.

A previous RCT on GBS from the US showed a beneficial effect with PE rate of 40-50 ml/kg/session, for 3 to 5 sessions in 7 to 14 days, which comes to a total PE volume of 120-250 ml/kg.[7] The first French RCT on adult GBS patients showed beneficial effect of 4 PE sessions [2 plasma volume (3.5 L) per PE session] over 8 days and in range, 6 – 12 L plasma was removed per patient.[4] Subsequent French RCT with PE dose escalation showed, 2 PE sessions [1.5 plasma volume per PE session] are beneficial in mild to moderate GBS cases but less effective than 4 PE sessions in severe GBS cases and 6 PE sessions are as effective as 4 PE sessions in severe cases of GBS.[5] In this RCT the exact total plasma volume exchanged per patient was not mentioned, but the authors indicated that the rate of plasma exchange was 40-ml/kg body weight per PE session. As to that a 60-70 kg person should have an exchange of 2.4 L-2.8 L per session and the therapeutic range of plasma volume to be exchanged would be 5.6 L to 11.2 L ml (2 to 4 PE sessions).

During the piloting of the SVPE procedure we assessed that removal of 1 L of patient plasma could be feasible in a day. Therefore we defined our target plasma volume of 8 L to be removed in 8 days. The median total PE volume and rate in SVPE was 8.4 L and 140 ml/kg, which is at the lower range as compared to both the French and American RCT on PE for adult GBS patients. We were able to remove >120 mL/kg plasma in 80% of patients, which should provide a therapeutic effect.[37] Notably, the body weight of our patients may be lower than that of patients

in western countries. In addition, SVPE was complete within 8 days, shorter than the usual time required for a full session of PE (10 to 12 days).

Replacement fluid used in SVPE was FFP. We have several justifications in favour of using FFP instead of human albumin or other available colloidal solutions available in Bangladesh. First FFP is safe in terms of microbiological safety since stringent screening for viral and bacterial contamination was performed before infusion. Second, in contrast to human albumin and colloid solutions, FFP contains normal human IgG that could contribute to the beneficial immunotherapeutic effect in GBS. FFP was previously used as replacement fluid in large PE trials, quintessentially with the same volume (half the volume of replacement fluid) we used in SVPE.[4 5] SVPE treated GBS patients received approximately half the amount of IgG from the FFP used as replacement fluid compared to the total IVIg doses traditionally used in GBS (2gm/kg). Third, FFP contains all human plasma proteins that helps preservation of plasma colloid osmotic pressure and prevents formation of oedema and hypotension. Lastly FFP is much cheaper than commercial human albumin.

In each day three units of FFP were transfused as replacement fluid after the last session of SVPE and in the initial two to three sessions, normal saline was used as replacement fluid. This was done to achieve the maximum immunotherapeutic effect of FFP as SVPE was not resumed before the next day and the IgG in FFP remained in the circulation overnight for a longer period of time (10 to 12 hours). However due to long half life of IgG, a substantial amount of IgG present in FFP were probably washed away due to repeated plasma removal both during SVPE and by conducting standard PE.

In GBS, treatment with modified methods of PE done previously, were device based and done on limited number of GBS patients. In one study on 25 GBS patients from India, daily removal of

small volume of plasma (10-15 ml plasma/kg body weight) for duration of median 3 days using traditional PE machine was shown to be clinically beneficial.[38] In another study from the same country, 12 GBS patients were treated with PE over 10 days using different PE-machine kit (REF627 kit from Haemonetics Corporation Limited on MCS+ machine) where authors claimed clinical improvement, however the main focus was on cost effectiveness and the total plasma volume exchanged per patient was not mentioned.[39] Nevertheless these methods are based on specific devices those are not in common practice, nor the trained personnel for these are available in the developing countries.

Important observations in terms of secondary endpoints were transient hypotension, transfusion reaction to FFP and minor bleeding through the CVC insertion site. Hypotension is a common complication during traditional PE that affects nearly half of patients.[5] Spells of hypotension during SVPE were more frequent during the three to four days after initiation of SVPE, and could be easily corrected by rapid infusion of 300-400 mL saline (Fig. 1). The hypotension could possibly be explained by hypovolemia due to drawing blood or as a result of the compromised autonomic nervous system in patients with GBS. As SVPE proceeded, hypotensive spells were encountered less frequently despite drawing the same volume of blood, which may in part be explained by adaptation of the vasomotor system or recovery from autonomic dysfunction. Minor bleeding through the CVC insertion site occurred in 50% of patients and could be controlled by applying a simple pressure pack over the CVC insertion site in most cases; mild prolonged PT was noted in 30% (3/10) patients. However, spontaneous bleeding usually occurs if the PT is more than 2.5 times prolonged and PC is < 0.50 lac/μL.[40] Movement of the limb where the CVC was placed may have caused traction on the CVC and contributed to local bleeding in the other seven patients. Haematuria is not uncommon in patients with a UTI, as may have occurred in one SVPE treated patient; traumatic traction of the urinary catheter may cause haematuria in two

other catheterized SVPE-treated patient taking oral aspirin, who had haematuria and sterile urine. We also monitored the major organ function and biochemical status of the patients treated with SVPE. No patients experienced hepatic or renal impairment. One patient developed anaemia and hypoalbuminemia; this patient had severe sepsis, a common cause of anaemia and hypoalbuminemia in critically ill patients admitted to an ICU (patient 11, Fig. 1). Electrolyte imbalances were detected in 15% of the SVPE-treated patients with GBS, and were mild, subclinical and easily corrected.

The median reported durations to recovery of independent walking in patients with GBS in large-scale RCTs after PE are 53, 52 and 70 days[4 5 7]; compared to 30 days in our patients treated with SVPE. Moreover, 60% of the patients with GBS treated with SVPE were able to walk independently at four weeks, whereas 20% of patients with GBS acquired independent walking ability at four weeks after traditional PE. However, these differences may possibly be due to the small sample size and variations in demographic and neurophysiological characteristics between cohorts. Finally, SVPE was completed in all 20 patients and no patients died.

Limitations of SVPE

SVPE is a time-consuming and labour-intensive procedure, which is a limitation. We used multiple thin-lumen tubing systems interconnected with a multichannel connecter device, which may increase the chance of blood coagulating within the tubing system. Coagulation may require manipulation or replacement of the tubing to ensure free flow of blood and saline. Such handling could increase the chance of microbial contamination. A single continuous wide-lumen tubing system (SVPE kit) could resolve this problem. Most importantly, personnel conducting the SVPE procedure should maintain proper aseptic technique, which can sometimes be challenging in developing countries. Furthermore, other adaptions such as provision of a larger blood bag or

increasing the number of days for SVPE could be considered to increase the plasma exchange rate.

Clinical implications and future research

Despite the limitations, our study showed SVPE is a safe and feasible treatment for GBS in a resource-limited setting where IVIg or PE are either unavailable or unaffordable. Specifically, the poorest 20% of the world's population (1.8 billion people) who typically earn less than 10 US$ per day and who are not covered by a national health insurance system may benefit. Considering the incidence of GBS is 2/100,000 in developing countries, approximately 40,000 patients could potentially benefit from SVPE every year, worldwide. In the future, a multicentre RCT is required to assess the clinical efficacy of SVPE for patients with GBS. If proven effective, SVPE could be an affordable and easily available alternative plasma exchange technique in low-income countries for patients with GBS and other disorders, who at present cannot afford standard PE due to its high cost and unavailability.

Declarations

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Authors' contributions: BI, PVD, BJ, QDM, ZI, and HPE conceived the study design and sample size of the study. MV, MVJ, SR, and HPE contributed to the infection safety guidelines in the study design. BI and QDM conducted the study and BI collected and analysed the data and drafted the manuscript. All authors have critically revised the manuscript and have read and approved the final manuscript.

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Data sharing: Extra data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi: 10.5061/dryad.55nb389

Transparency: The corresponding author affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1: Demographic and clinical characteristics of the 20 patients with GBS included in this small volume plasma exchange (SVPE) study at entry

Characteristic		Value
Demography		
Sex [males: females (ratio)]		13:7 (1.85)
Age (years) ¶		33 (18 - 55)
Body weight (kg) ¶		60 (50 -72)
Antecedent events ‡ (total)		18 (90%)
Diarrhoea		10 (50%)
Respiratory infection		5 (25%)
Fever		3 (15%)
Days from antecedent events to weakness ¶		7 (3 - 30)
Days between onset of weakness to admission ¶		7 (2-12)
Neurological deficits at entry		
Weakness in arms and legs		20 (100%)
Cranial nerve deficits		12 (60%)
Decreased deep tendon reflexes		20 (100%)
Sensory involvement		5 (25%)
GBS disability score §	4	19 (95%)
	5	1 (5 %)
Severity of weakness (MRC sum-score) ¶		20 (0-29)
Autonomic dysfunction		11 (55%)

¶ Median (range); † increased protein level (> 45 mg/dL) in combination with CSF cell count < 50/µL; CSF = cerebrospinal fluid; NCS = nerve conduction study; ‡ symptoms of an infection in the four weeks preceding the onset of weakness; § GBS disability score (0 - 6) = 0: healthy state; 1: minor symptoms and capable of running; 2: able to walk 10 meters or more without assistance but unable to run; 3: able to walk 10 meters across an open space with help; 4: bedridden or chair-bound; 5: requiring assisted ventilation for at least part of the day; 6: dead.

689 Table 2: Treatment characteristics and complications associated with SVPE in the 20 patients
690 with GBS

Characteristic/complication	Value
Treatment characteristics	
Number of sessions of SVPE per patient ¶	30 (24 - 42)
Volume of plasma removed per patient ¶	8.4 (6.3 – 9.6)
Plasma exchange rate (mL/kg) ¶	140 (110-175)
Time between hospital admission and SVPE (days) ¶	8 (5-10)
Time between onset of weakness and start of SVPE (days) ¶	8 (5-10)
Need to stop SVPE due to poor hemodynamic tolerance	0/20 (0%)
Need for blood transfusion for anaemia	1/20 (5%)
Reduction of anticoagulant drug dose for bleeding	3/20 (15%)
Temporary withdrawal of antiplatelet drug for bleeding	4/20 (20%)
Increased anticoagulant drug dose to continue SVPE	1/20 (5%)
CVC blockade/replacement	0/20 (0%)
Complications during SVPE	
Infection	
Leukocytosis	7/20 (35%)
CLABSI §	6.25
VAP §	136.4
CAUTI §	40
Severe sepsis	1/20 (5%)
Antimicrobial agents used	6/20 (30%)
Bleeding and coagulation	
Bleeding from CVC insertion site	10/20 (50%)
Bleeding from mucosal area	3/20 (15%)
Prolonged BT (BT > 10 min)	0/20 (0%)
Prolonged CT (CT > 15 min)	0/20 (0%)
Prolonged PT (PT > 14 sec) ¶	6/20 (30%) [15-19 sec]

Prolonged aPTT (aPTT > 40 sec) ¶	3/20 (15%) [51-240 sec]
Other complications	
Saline responsive hypotension	10/20 (50%)
Anaemia (Hb < 8 gm/L)	2/20 (10%)
Thrombocytopenia (PC < 1.5 lac/µL) ¶	6/20 (30%) [0.79-1.3 lac/µL]
Jaundice (serum bilirubin > 1.2 mg/dL)	0/20 (0%)
Renal impairment (serum creatinin > 1.2 mg/dL)	0/20 (0%)
Hyponatraemia (serum Na^+ < 135 mEq/L)	1/20 (5%) [126 mEq/L]
Hypokalaemia (serum K^+ < 3.5 mEq/L) ¶	3/20 (15%) [2.6-3.2 mEq/L]
Hypoalbuminemia (serum albumin > 35 gm/L) ¶	4/20 (20%) [26-32 gm/L]
Hypocalcaemia (serum Ca^+ < 2.2 mmol/L) ¶	3/20 (15%) [1.89-1.98 mmol/L]
Hypomagnesaemia (serum Mg^+ < 75 mEq/L) ¶	1/20 (5%) [73 mEq/L]
Hypersensitivity/transfusion reaction to FFP	4/20 (20%)

¶ Median (range); § rate per 1000 device days; CLABSI: central line-associated bloodstream infection; VAP: ventilator-associated pneumonia; CAUTI: catheter-associated urinary tract infection; CVC: central venous catheter; BT: bleeding time, CT: clotting time; PT: prothrombin time; APTT: activated partial thromboplastin time; FFP: fresh frozen plasma.

Table 3: Neurological outcomes of the 20 patients with GBS after SVPE

Clinical outcome	1 month	2 months	3 months	6 months
Cranial nerve involvement	7/20 (35%)	6/20 (30%)	4/20 (20%)	2/20 (10%)
Autonomic involvement	3/20 (15%)	3/20 (15%)	0/20 (0%)	0/20 (0%)
Sensory dysfunction	1/20 (5%)	1/20 (5%)	1/20 (5%)	1/20 (5%)
GBS disability score¶	0 = 0	0 = 1	0 = 1	0 = 2
	1 = 3	1 = 6	1 = 7	1 = 7
	2 = 9	2 = 6	2 = 6	2 = 5
	3 = 2	3 = 1	3 = 1	3 = 3
	4 = 3	4 = 5	4 = 5	4 = 3
	5 = 3	5 = 1	5 = 0	5 = 0
MRC sum score † ⁎	47 (0-60)	49 (0-60)	53 (6-60)	58 (22-60)
ONLS ‡ ⁎	4 (1-12)	3 (0-12)	3 (0-12)	2 (0-10)
R-ODS § ⁎	26 (0-41)	33 (0-45)	37 (0-45)	38 (0-46)

⁎ Median (range); ¶ GBS disability score (0 - 6) = 0: healthy state, 1: minor symptoms and capable of running, 2: able to walk 10 meters or more without assistance but unable to run, 3: able to walk 10 meters across an open space with help, 4: bedridden or chair-bound, 5: requiring assisted ventilation for at least part of the day, 6: dead; † MRC sum score: Medical Research Council sum score; ‡ ONLS: Overall Neuropathy Limitation Scale [22]; § R-ODS: Rash-built Overall Disability Score [23]

Figure 1: Feasibility of SVPE and associated complications for the 20 individual patients with GBS.

SVPE: small volume plasma exchange, HAI: hospital acquired infection, V: ventilator-associated pneumonia, B: central line-associated blood stream infection, U: catheter-associated urinary tract infection, [A] measured in litres, ●: spell of hypotension (systolic BP < 90 mm Hg), ◊: CVC insertion site bleeding, ▲: hypersensitivity to fresh frozen plasma, shaded squares: pyrexia due to bacterial infection, dotted squares: pyrexia due to suspected viral infection, M: onset of mechanical ventilation, C: urinary catheterization.

Figure 2: Hospital-acquired infections and use of antibiotics in the 20 patients with GBS receiving SVPE compared to the 24 hospital control patients without GBS treated in an ICU with a CVC who did not receive SVPE.

■ SVPE (n = 20): twenty patients with GBS aged ≥ 18-years-old who were bedbound (GBS disability score ≥ 4) received small volume plasma exchange (SVPE) within 2 weeks of the onset of weakness. ⊡ Non-SVPE (n=20): twenty-four patients aged ≥ 18-years-old with a diagnosis other than GBS who required a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units in the same period as the patients with GBS received SVPE; ∗ $p < 0.0001$.

Figure 3: Kaplan-Meier estimate (with 95% confidence limits) of the cumulative incidence of restoration of independent walking ability in patients with GBS treated with SVPE.

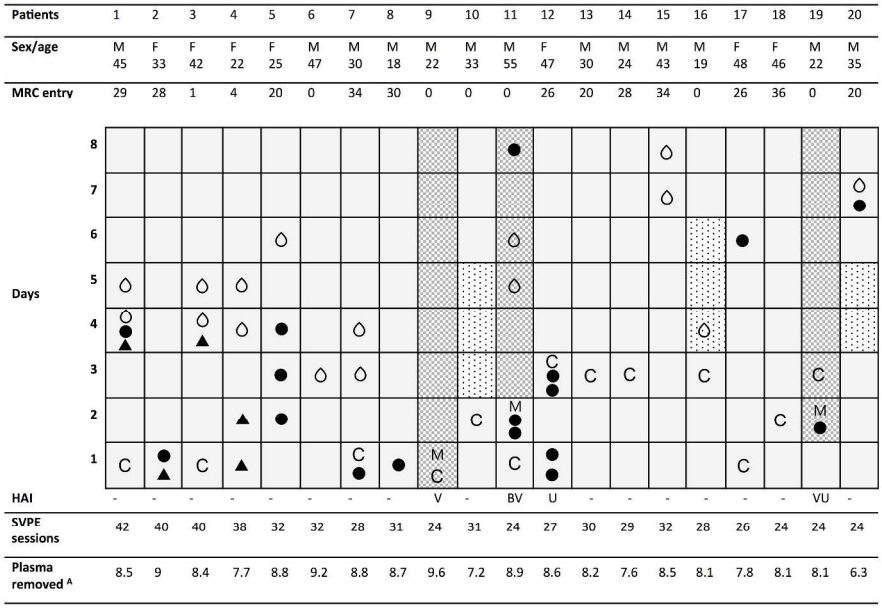
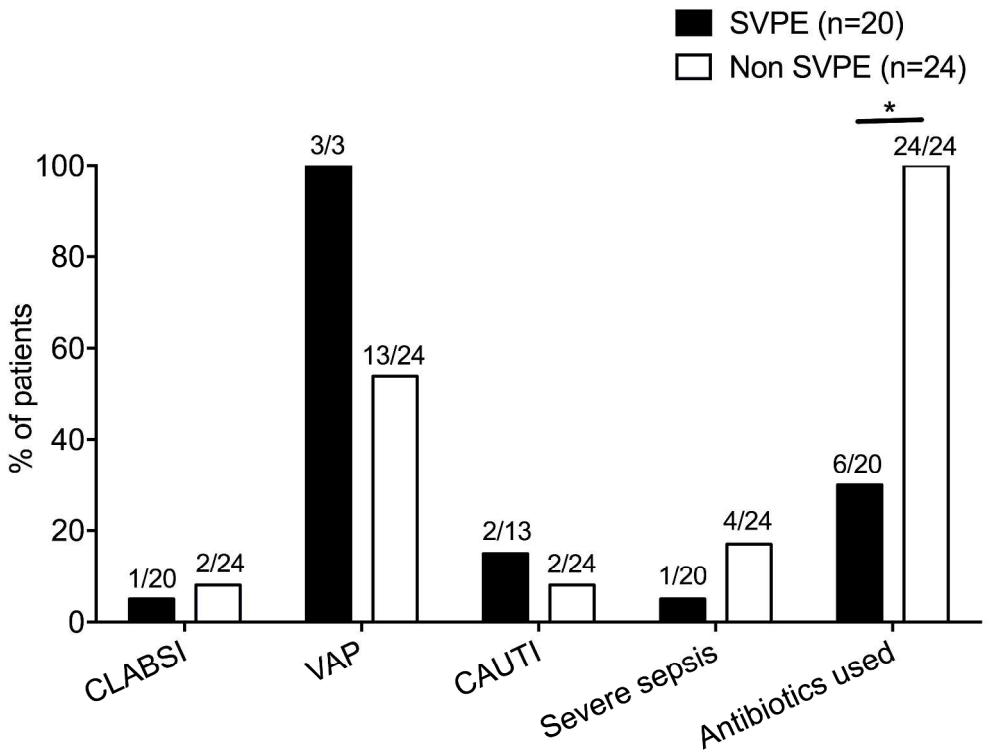


Figure 1: Feasibility of SVPE and associated complications for the 20 individual patients with GBS. SVPE: small volume plasma exchange, HAI: hospital acquired infection, V: ventilator-associated pneumonia, B: central line-associated blood stream infection, U: catheter-associated urinary tract infection, A measured in litres, black dot: spell of hypotension (systolic BP < 90 mm Hg), empty drop: CVC insertion site bleeding, black triangle: hypersensitivity to fresh frozen plasma, shaded squares: pyrexia due to bacterial infection, dotted squares: pyrexia due to suspected viral infection, M: onset of mechanical ventilation, C: urinary catheterization.



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■ SVPE (n = 20): twenty patients with GBS aged ≥ 18-years-old who were bedbound (GBS disability score ≥ 4) received small volume plasma exchange (SVPE) within 2 weeks of the onset of weakness. ⊡ Non-SVPE (n=20): twenty-four patients aged ≥ 18-years-old with a diagnosis other than GBS who required a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units in the same period as the patients with GBS received SVPE; * $p < 0.0001$.

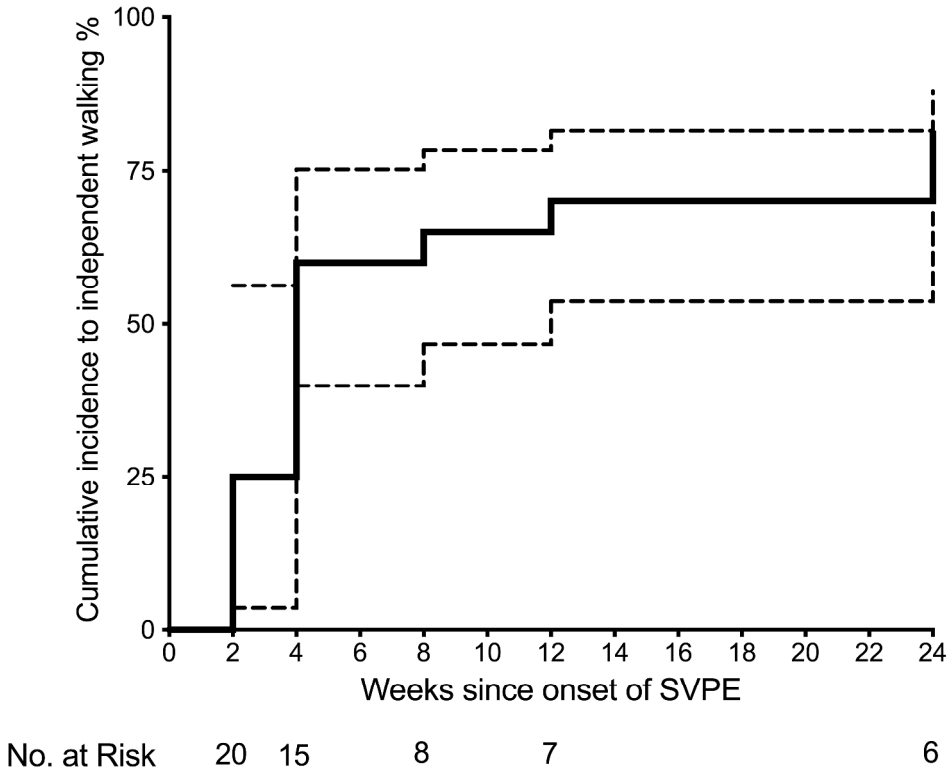
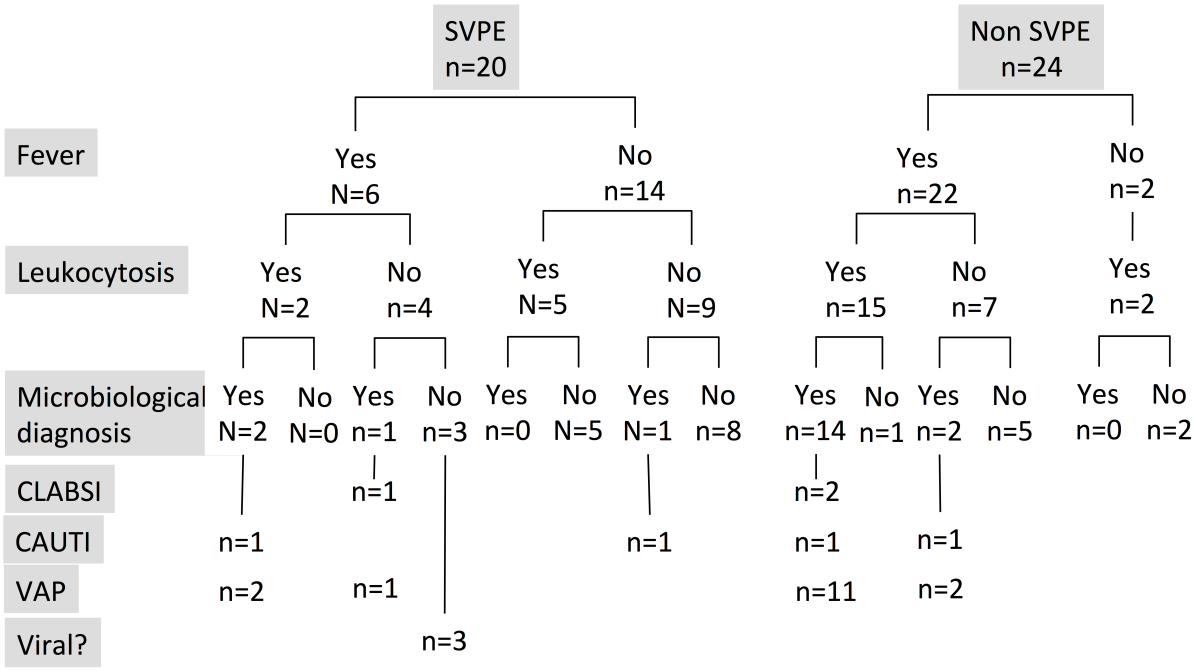


Figure 3: Kaplan-Meier estimate (with 95% confidence limits) of the cumulative incidence of restoration of independent walking ability in patients with GBS treated with SVPE.

Supplementary Figure: Hospital-acquired infections in the 20 patients with GBS treated with SVPE and the 24-hospital control patients without GBS.



SVPE: small volume plasma exchange, CLABSI: central line-associated blood stream infection, CAUTI: catheter-associated urinary tract infection, VAP: ventilator-associated pneumonia.

2017 CONSORT checklist of information to include when reporting a randomized trial assessing nonpharmacologic treatments (NPTs)*. Modifications of the extension appear in italics and blue.

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
Title and abstract					
	1a	Identification as a randomized trial in the title	NA (Non-randomized)		
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3, 4, 5	Refer to CONSORT extension for abstracts for NPT trials	3, 4, 5
Introduction					
Background and objectives	2a	Scientific background and explanation of rationale	6		
	2b	Specific objectives or hypotheses	6, 7		
Methods					
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7	When applicable, how care providers were allocated to each trial group	NA
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	No changes to methods after trial commencement		
Participants	4a	Eligibility criteria for participants	7, 8	When applicable, eligibility criteria for centers and for care providers	NA
	4b	Settings and locations where the data were collected	7		
Interventions†	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7, 8	Precise details of both the experimental treatment and comparator	7, 8
	5a			Description of the different components of the interventions and, when applicable, description of the procedure for tailoring the interventions to individual participants.	9
	5b			Details of whether and how the interventions were standardized.	8, 9

Cite as: *Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40–7.*

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
	5c.			Details of whether and how adherence of care providers to the protocol was assessed or enhanced	8, 9
	5d			Details of whether and how adherence of participants to interventions was assessed or enhanced	NA
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9		
	6b	Any changes to trial outcomes after the trial commenced, with reasons	No changes to trial outcomes after the trial commenced		
Sample size	7a	How sample size was determined	9	When applicable, details of whether and how the clustering by care providers or centers was addressed	NA
	7b	When applicable, explanation of any interim analyses and stopping guidelines	10		
Randomization:					
- Sequence generation	8a	Method used to generate the random allocation sequence	NA (Non-randomized)		
	8b	Type of randomization; details of any restriction (such as blocking and block size)	NA (Non-randomized)		
- Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	NA (Non-randomized)		
- Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	NA (Non-randomized)		
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Blinding was not possible	If done, who was blinded after assignment to interventions (e.g., participants, care providers, those administering co-interventions, those assessing outcomes) and how	Blinding was not possible

Cite as: *Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40–7.*

Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
	11b	If relevant, description of the similarity of interventions	7, 8		
	11c			If blinding was not possible, description of any attempts to limit bias	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10	When applicable, details of whether and how the clustering by care providers or centers was addressed	NA
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NA		
Results					
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	11	The number of care providers or centers performing the intervention in each group and the number of patients treated by each care provider or in each center	Single center study
	13b	For each group, losses and exclusions after randomization, together with reasons	No losses and exclusions after inclusion		
	13c			For each group, the delay between randomization and the initiation of the intervention	11
	new			Details of the experimental treatment and comparator as they were implemented	11-16
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7		
	14b	Why the trial ended or was stopped	NA (Trial completed)		
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1	When applicable, a description of care providers (case volume, qualification, expertise, etc.) and centers (volume) in each group.	NA
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11-12		

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Section/Topic Item	Checklist item no.	CONSORT item	Page no	Extension for NPT trials	Page no
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12-16		
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA		
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	15		
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12-15		
Discussion					
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	20-21	In addition, take into account the choice of the comparator, lack of or partial blinding, and unequal expertise of care providers or centers in each group	NA
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	16-20	Generalizability (external validity) of the trial findings according to the intervention, comparators, patients, and care providers and centers involved in the trial	16-20
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16-20		
Other information					
Registration	23	Registration number and name of trial registry	4		
Protocol	24	Where the full trial protocol can be accessed, if available	Manuscript reference no: 17		
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	22		

**Additions or modifications to the 2010 CONSORT checklist. CONSORT = Consolidated Standards of Reporting Trials*
†The items 5, 5a, 5b, 5c, 5d are consistent with the Template for Intervention Description and Replication (TIDieR) checklist

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Table: Required documents of the safety and feasibility study of the small volume plasma exchange (SVPE) for Guillain-Barré syndrome patients for the World Health Organization Trial Registration Data Set

	Item/Label	Description
1	Primary Registry and Trial **Identifying** Number	Clinicaltrials.gov NCT02780570
2	Date of Registration in Primary Registry	May 23, 2016
3	Secondary Identifying Numbers	International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) Protocol Number: PR-15086, Version no. 3, Date: 09/12/2015
4	Source(s) of Monetary or Material Support	GBS/CIDP Foundation International Fondation Mérieux: (Small Grants Program 2015)
5	Primary Sponsor	GBS/CIDP Foundation International
6	Secondary Sponsor(s)	Fondation Mérieux: (Small Grants Program 2014)
7	Contact for public queries	MD. BADRUL ISLAM Email: bislamdmch@gmail.com Telephone no: +880 1712 89 0172 Postal address: Dr. Badrul Islam

		Research trainee and PhD Fellow Laboratory Sciences and Services Division (LSSD) Icddr,b Dhaka, Bangladesh
8	Contact for scientific queries	MD. BADRUL ISLAM Principal Investigator (PI) Email: bislamdmch@gmail.com Telephone no: +880 1712 89 0172 Postal address: Dr. Badrul Islam Research trainee and PhD Fellow Laboratory Sciences and Services Division (LSSD) Icddr,b Dhaka, Bangladesh
9	Public title	Small volume plasma exchange for Guillain-Barré syndrome
10	Scientific title	Small volume plasma exchange for Guillain-Barré syndrome in low-income countries: a safety and feasibility study
11	Countries of Recruitment	Bangladesh
12	Health condition(s) or problem(s) studied	Guillain-Barré syndrome (GBS)
13	Interventions	*Small Volume Plasma Exchange (SVPE)* A loading dose of low-molecular weight heparin (1.5 mg/kg) will be given subcutaneously at least two hours

before initiation of SVPE; the same dose will be administered once daily or divided into two equal doses daily for eight days or until SVPE is completed. Whole blood (7 mL/kg body weight) will be drawn from the central venous catheter into the blood transfusion bag in each session. The blood bag will be hung beside the patient for 2.5 h on a saline stand and left uninterrupted to allow plasma and blood cells to separate. The blood cells will be infused back into the patient and plasma will be discarded and replaced with fresh frozen plasma and colloid solution alternately (in equal volumes) via the closed-circuit SVPE kit illustrated in. In case of excessive clotting (bleeding time reduction of > 50% of baseline for that patient), aspirin (600 mg) will be administered orally at least two hours before the next SVPE session and continued thereafter at 150 mg orally/day until SVPE is completed. One blood bag will be used each day, with a total of six sessions/day. A total of 48 sessions will be performed over eight days, removing approximately 8000 mL plasma in total.

Central venous catheterized patients without GBS

To compare the safety of SVPE in patients with GBS in the context of the background risk of central line-associated blood stream infection (CLABSI) at the study intensive care (ICU) and high-dependency care (HDU) units, the incidence of CLABSI will be assessed in a control group of adult patients with a diagnosis other than GBS admitted to the same ICU and HDU units in the same period of time the patients with GBS will be enrolled for SVPE. We will assess the rate of CLABSI in

		patients aged ≥ 18-years-old requiring a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units.
14	Key Inclusion and Exclusion Criteria	*Inclusion criteria for SVPE in GBS patients* 1. Patients aged ≥ 18-years-old fulfilling the diagnostic criteria for GBS of the National Institute of Neurological and Communicative Disorders and Stroke (NINDS) 2. Unable to walk unaided for more than 10 meters (GBS disability score ≥ 3) 3. Presented within 2 weeks of the onset of weakness 4. Unable to afford standard treatment with IVIg or PE. *Exclusion criteria for SVPE in GBS patients* 1. Patients with severe or terminal concomitant illness 2. Evidence of healthcare-associated infection on admission (except for aspiration pneumonia) 3. Previous history of severe allergic reaction to properly matched blood products and pregnant women will be excluded from the study. *Inclusion criteria for patients without GBS* 1. Patients aged ≥ 18-years-old 2. Requiring a CVC for > 2 to ≤ 8 calendar days after admission to the same ICU and HDU units in the same period of time the patients with GBS enrolled for SVPE. *Exclusion criteria for patients without GBS*

		1. Patients with healthcare-associated infection present on admission (except aspiration pneumonia) 2. Pregnant women
15	Study type	*Type of the study*: Interventional *Method of allocation:* Non-randomized *Masking:* Non-masked *Assignment:* Parallel arm • SVPE in patients with GBS • Rate of CLABSI in patients without GBS *Purpose:* Safety and feasibility of SVPE
16	Date of first enrolment	February 20, 2016
17	Target sample size	SVPE in patients with GBS = 20 Rate of CLABSI in patients without GBS = ≥ 20
18	Recruitment status	Completed: • Twenty cases of GBS have been successfully treated with SVPE and 24 control cases without GBS have been recruited.
19	Primary Outcome(s)	*Primary outcome of safety*: 1. Number of patients with GBS treated with SVPE developing severe sepsis or septic shock due to central line associated blood stream infection (CLABSI) as per standard guideline (Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central line-associated Bloodstream Infection); CDC Device-associated Module, BSI. January 2017) 2. Occurrence of venous thrombosis in the limb

		where the CVC is placed. Venous thrombosis will be assessed according to Wells criteria (*Philip S. Wells et al. Evaluation of d -Dimer in the Diagnosis of Suspected Deep-Vein Thrombosis; N Engl J Med 2003;349:1227-35*) *Primary outcome of feasibility*: 1. Ability to remove at least eight litres of plasma by SVPE over eight days.
20	Secondary Outcome(s)	*Secondary outcome of safety*: 2. Relative risk of CLABSI due to SVPE compared to CLABSI in control patients without GBS treated using a CVC 3. Hemodynamic instability during the SVPE procedure (variations in systolic blood pressure greater than 30 mmHg or sudden bradycardia involving a reduction in heart rate by more than 20 beats per min within 30 min of starting SVPE or an increase in heart rate above 120 beats per min) 4. Development of anaemia (Hb <7 gm/dL) or serious haemorrhage requiring blood transfusion. *Secondary outcome of feasibility*: 1. Rate of CVC occlusion during the SVPE procedure 2. The healthcare personnel's acceptability and

		satisfaction with the SVPE procedure and any unanticipated events compromising the SVPE procedure as assessed using a standard questionnaire. 3. Neurological outcome will be assessed in terms of improvement in GBS disability score and MRC sum score at discharge and up to 4 weeks after entry.